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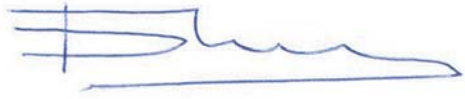
On behalf of the “International Journal of Interventional Cardioangiology” and in my personal capacity I want to present my cordial congratulations to the Department of Endovascular Methods of Diagnosis and Treatment of the Orenburg Regional Clinical hospital oh the occasion of its 20th anniversary. Twenty years – it’s quite a long time for such young profession as endovascular surgery, and there are few teams in our country who do not only act in the field of management of various cardiovascular diseases, but also conduct new research and improve the application of the obtained results in practice. Obviously, in large part the achievements of the Department are due to its Head – the Honored Doctor of RF, Professor Viktor Demin. Under his guidance, the staff of the Department conduct an intensive and fruitful practical and research work.

The research and practical Symposium “Methods of Intravascular Imaging” will sum up some of the results of this work. I wish my colleagues to stay strong in the pursuit of their goals and to continue to do everything for further development of our profession.

Editor-in Chief
of the “International Journal
of Interventional Cardioangiology”
Corresponding member of RAS



D.G. Iosseliani

Dear Friends and Colleagues,

We are glad to present in this issue of the Journal certain papers, which in some kind summarize the researches performed in our Department during the 20 years of its activities. The character of the work in a multiprofile hospital, acting also as a regional vascular center, significantly differs from this one of the special centers or research institutes. Nevertheless, from the first days of its existence, the Department of Endovascular Methods of Diagnosis and Treatment of the Orenburg Regional hospital, besides continuously increasing clinical practice, conducts intensive research work.

The presented articles give a rather complete idea of the spectrum of the main research interests of our Department. Despite their diversity, including the recanalization of chronic total coronary occlusions, the management of in-stent restenosis using drug-eluting balloons, the implantation of resorbable scaffolds, the treatment of bifurcations, the embolization of patent ductus arteriosus: all these works are united by the broad use of various methods of intravascular imaging – optical coherence tomography and intravascular ultrasound. Meanwhile even the whole issue of the Journal cannot cover all the topics of our research. We hope to continue it.

We are deeply grateful to the Editorial Board of the "International Journal of Interventional cardioangiology" and, particularly, to the Editor-in-Chief, Professor David G. Iosseliani, who supported us in our unusual initiative and offered us the pages of the whole issue of the Journal.

Viktor V. Demin, MD

Head, Department of Endovascular Methods of Diagnosis and Treatment, Orenburg Regional Clinical Hospital, Professor, Chair of Therapy, Orenburg State Medical University

Recanalization of Chronic Coronary Total Occlusions: Basic Terms of Success

V.V. Demin, S.A. Dolgov, M.M. Murzaykina, A.V. Demin, A.V. Grigorev, A.S. Kodyakov, E.A. Ilnitskaya*

Orenburg Regional Clinical Hospital, Orenburg

The article presents a retrospective analysis of 1256 recanalizations of chronic coronary total occlusions. Recanalizations averaged 19.0% of all elective coronary interventions. The immediate recanalization success rate for all these years averaged 88.3% including 92% in the last 4 years. The features of interventional technique in recent years are predominant application of bilateral transradial access, priority of Shinobi and Gaia coronary guidewires, retrograde access in 1,6% of cases only), frequent use of intravascular visualization during recanalization, high attention to selection of optimal size and adequate stent implantation.

Key words: *chronic coronary total occlusion, recanalization, intravascular imaging, intravascular ultrasound, optical coherence tomography, coronary stenting.*

Objective. To perform a retrospective analysis of factors impacting the success of recanalization of coronary chronic total occlusions and assess the most effective techniques used in daily practice.

Methods. 1256 recanalizations of the coronary chronic total occlusions were performed within the period from 1998 to June 2015 including 602 interventions (47.9%) for the last 4.5 years. For practical purposes, it is supposed to determine three populations depending on visualization of the affected segment. The first type (25% of all occlusions) includes segmental occlusion with antegrade flow or pronounced bridge collaterals. The second type (43.8%) presents occlusion with intra-system or well pronounced inter-system collaterals. The third type (31.2%) has slightly marked inter-system collaterals and/or no intra-system collaterals.

Results. Recanalizations amounted to 19.0% of all elective coronary interventions. IVUS was used in 17.5% of all recanalizations. The majority of procedures (55%) were performed after recanalization and predilation. Follow-up after stent implantation accounted for one third of IVUS procedures. Over the last 4 years, OCT was used in 22% of interventions at the final stage for stent implantation quality control. Within the period from 1999 to 2015, the immediate success rate of recanalization was 88.3% including 92% over 2011–2015 years.

Conclusions. The modern techniques and balanced approaches to selection of intervention strategy give a high success rate of recanalization of coronary chronic total occlusions even with the low rate of retrograde access. The intravascular imaging at different stages of intervention contributes to good immediate and long-term outcomes. The selection of optimal size and adequate stent implantation play no less important role for the intervention outcome than recanalization stage itself.

Introduction

Coronary chronic total occlusions remain one of the most difficult sections of interventional cardiology. A significant development of technologies and, primarily, the appearance of new coronary guidewires including specialized ones for this pathology have led to impressive progress in recent years. A certain standardization of the intervention is achieved thanks to the CTO societies. However, the intervention results vary significantly from clinic to clinic, and the success rate of recanalization is from 60 to 95%. In recent years, the primary success rates of recanalization have increased significantly. Within the period from 1992 to 2002, the mean

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rate of successful recanalization in Thoraxcenter (Rotterdam) was 65.1% (1). When EuroCTO was founded in 2006, its 15 members had the success rate of chronic occlusion recanalization from 62 to 85%, 75.1% on average (2). The Japanese registry J-CTO (12 sites, 528 lesions intervened in 2006–2007) reported the mean recanalization success rate of 86.6%, while it varied from 97.0% to 73.6% depending on the J-CTO score (3). In accordance with the EuroCTO consensus (4), the operator should select the cases for recanalization in accordance with his/her experience to achieve success rate not less than in 80% of cases.

The challenge of chronic occlusions remains relevant and will be such for many years. Here, in our opinion, there are several quite neglected factors. Firstly, the techniques and approaches recommended by Japanese experts in chronic recanalization were specifically mythologized. Primarily, it concerns approaches to selection and sequence of coronary guidewires to be used, application of retrograde recanalization and various options of subintimal blood flow restoration. Secondly, the thesis on critical importance of coronary guidewire crossing for intervention success, although obvious, is quite questionable for after the most technically difficult part of the intervention, the operator implicitly relaxes and pays less attention to choice of optimal type and size of the stent and achievement of optimal angiographic results. Finally, the recanalization of coronary chronic total occlusion is perhaps the most individualized among the entire spectrum of coronary interventions. It is affected by both the choice of coronary guidewire (which is one of the most individualized tools), and preferences for access and recanalization technique, and frequency of intravascular imaging, and many other factors.

Materials and methods

Although some authors determine chronic total occlusions as those lasting for 15 days (5) or 1 month (6), we follow the EuroCTO opinion on more than 3 month duration of such lesions (7). There are two main types of coronary occlusions. The so-called functional occlusion (7) is characterized by minimal contrast penetration through the affected area without full filling of the vessel distal to the occlusion (TIMI I blood flow). The preserved microchannels or bridge collaterals contribute to antegrade filling. The “true” total occlusion is characterized with TIMI 0 blood flow and inability to visualize the distal part of the coronary artery. However, the intervention for functional occlusion is not always simpler. Hurried or incorrect guidewire manipulations can quickly damage antegrade blood flow turning an occlusion to the “true” one with modification of the entire plan of intervention.

For the purpose of recanalization tactics and subsequent tool selection for stenting, we determine three groups of patients depending on the nature of visualization of the affected segment, which in turn, depends mainly on the severity of intra- and intersystem collaterals. The first type includes segmental occlusion with antegrade blood flow or pronounced bridge collaterals. Besides, the entire occluded segment is well visualized in one frame. This type of lesion is generally consistent with the concept of functional occlusion (Fig. 1A). The second type is occlusion with intra- or well pronounced intersystem collaterals. It is possible to visualize the distal circulation but its assessment and judgments on the occlusion length can be inaccurate, typically, the lesion is more prolonged and total occlusion areas adjoin to stenoses of different degrees (Fig. 1B). Type 3 is characterized with no intrasystem collaterals and/or slightly pronounced intersystem collaterals. The measurement of length of the segment to be stented is impossible or inaccurate (Fig. 1C).

Some steps in intervention technique important, in our opinion, for the ultimate success should be emphasized.

The main techniques to overcome chronic total occlusions include sliding, drilling and penetrating. Sliding technique is mainly applicable for functional occlusions when the residual microchannels or secondary channels within the occlusion with signs of spontaneous recanalization should be found. The penetrating technique is often necessary to overcome the terminal plaque or exit from the false lumen to the true one while subintimal recanalization is performed. The drilling technique involving guidewire passage using gentle dosed rotations is the primary method of chronic total occlusion recanalization in our experience. It is manly a basis for selection of optimal guidewire for recanalization which is one of the most important aspects of the intervention. Coronary guidewires Shinobi and Shinobi plus, Cordis were used in the vast majority of our interventions. When Japanese guidewires and similar guidewires of other manufacturers appeared, many authors became to use Shinobi guide-

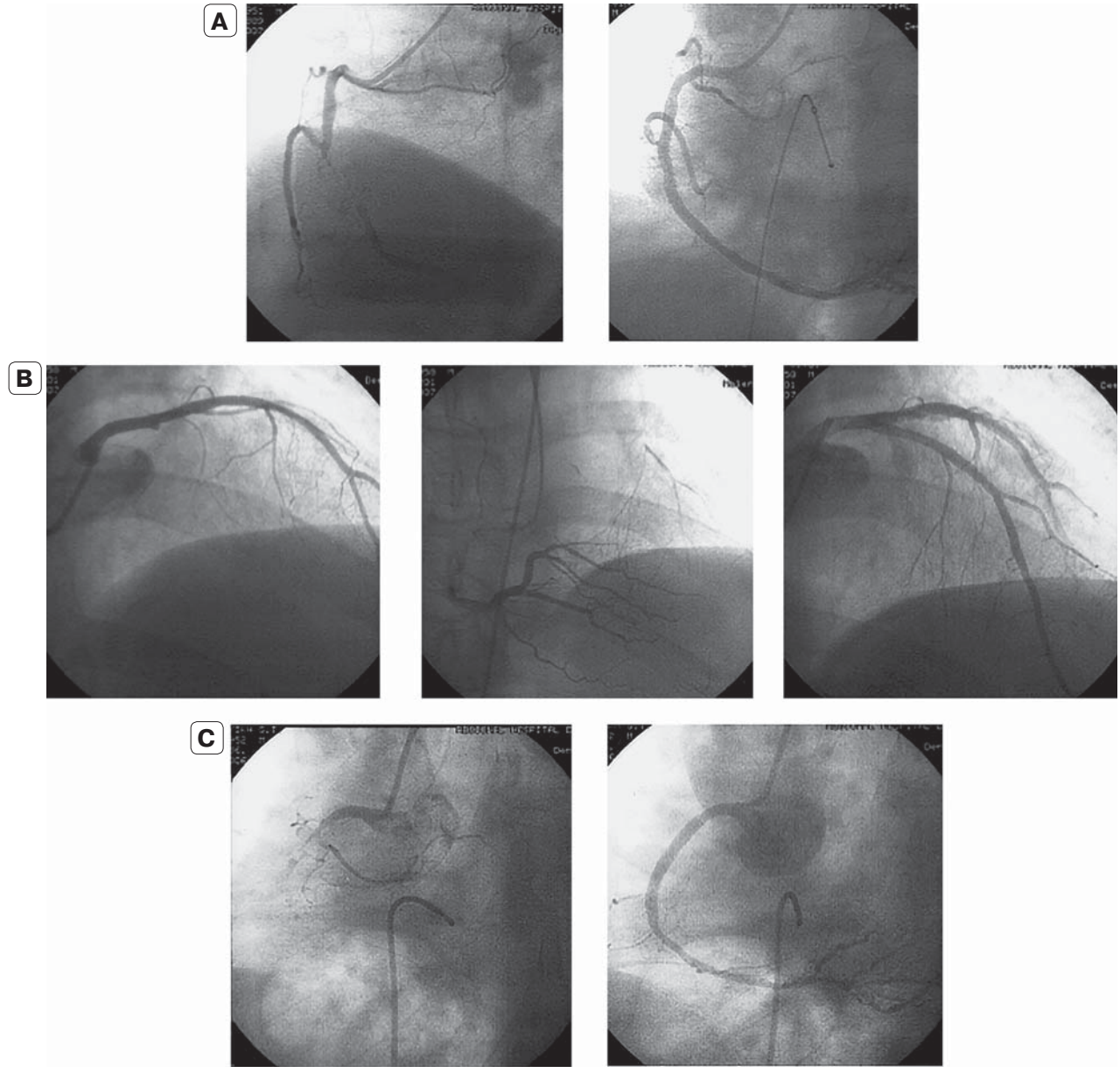

Figure 1. Working classification of the occlusions:
A – type 1 – segmental occlusion with antegrade blood flow or pronounced bridge collaterals;
B – type 2 – occlusion with pronounced intersystem collaterals;
C – type 3 – no inter-system collaterals and slightly pronounced intra-system collaterals. On the right, all frames demonstrate the recanalization results.

wires less often. The reasons which explain this situation include rigidity of the guidewire and high risk for arterial perforation. However, we consider this guidewire, if used by an experienced operator, a versatile tool combining many important properties necessary for coronary guidewires. The comparative studies by Abbott Vascular demonstrate that the Shinobi and Shinobi plus guidewires tips are less rigid than in most Progress (Abbott Vascular) and Miracle (Asahi Intecc) guidewires. Beside, the tip of the Shinobi guidewires is not sharpened (it increases penetrating ability). The real practice shows the perforating ability is significantly higher in such guidewires as JET and Progress (Abbott Vascular) and Gaia (Asahi Intecc), and, of course, the most “heavy” Conflanza guidewires (Asahi Intecc) compared to Shinobi. The impression of the total rigidity of the Shinobi guidewires is related to another property, i.e. high level of support exceeding support levels of most other guidewires excluding special guidewires with extra-support. High support is useful for balloons and stents delivery through difficult anatomical areas. With regard to arterial occlusions, on the one hand, it allows bet-

ter control of rotations, on the other, it transmits greater total force on the tip due to less deformation of the guidewire body. This combination of properties in one guidewire allows in most cases moving away from the so-called "step-by-step" recanalization technique when the intervention starts with a guidewire of the least penetrating power followed by gradual increase of impact. Ultimately, it has economic effect. At the same time, in our opinion, Shinobi guidewire is safer than the other approach when penetration guidewire with sharpened tip and hydrophilic coating is used immediately after intermediate guidewire.

Of course, the operator performing chronic total occlusion recanalization should have a variety of different tools including a panel of different guidewires. We have the majority of the most common modern coronary guidewires and selectively use them in our practice. A special attention should be paid to Gaia guidewires (Asahi Intecc) as they have 1-mm curved tip, very high manageability and precise feedback as well as three degrees of rigidity. Currently, thanks to these features, the Gaia guidewires are the tools of first choice in many cases. Gaia First being a non-polymeric guidewire, however, can be considered one of the best tools for sliding in functional occlusions. It is necessary to remember the significant tendency of the Gaia Second and Gaia Third guidewires to pass subintimally at the level of terminal plaque.

In addition to guidewire selection and ability to use it correctly, creation of conditions for stabilization of guiding catheter and coronary guidewire is critical for recanalization success. The guiding catheters of larger diameter are traditionally considered more stable and preferable for recanalization. Therefore, 7 F guiding catheters and transfemoral access naturally predominate. However, a switch to transradial access is the modern trend and we primarily use this access and 6F guiding catheters in the last two years. Approximately 20% of recanalizations performed via transradial access required additional methods of stabilization, i.e. balloon anchoring technique with inflation in one of the proximal lateral branches or vessel part proximal to the occlusion, or, less frequently, guidewire anchoring technique. In the past year, when Guidezilla guide extension catheter (Boston Scientific) appeared on market, we started to use it effectively to stabilize the entire system. The important factor for recanalization success is guidewire stabilization which increases its supporting strength and impact precision and allows penetration of the proximal plaque, primarily, near a lateral branch. The low-profile short balloon (1.2–2.0 mm × 8.0–12.0 mm) is routinely used. In some cases, especially if peripheral arteries are weakly filled via collaterals, microcatheter Corsair is used for support and subsequent recanalization.

The catheterization of the second artery for verification of the guidewire position is absolutely necessary for technically difficult recanalization of type 3 occlusions. However, we consider it reasonable to use the second access in type 2 and even type 1 occlusions when there are pronounced inter-system collaterals. As noted above, the reason is that guidewire manipulations can quite easily damage intra-system collaterals or microchannels. We use both bilateral radial access and combination of femoral and radial accesses.

Parallel guidewire technique is one of the important methods used in recanalization. Several issues should be considered when this technique is applied. Before introducing the second and subsequent guidewires one should clearly understand how far the previous one is from the true lumen and what direction and what level are required for the following guidewire to search for the lumen. A simple screwing of the second guidewire along the first one can only increase a spiral dissection when the second tool deflects in the other direction but within the same layer. Therefore, it is desirable to switch to parallel guidewire technique in a timely manner not waiting until the distal part of the vessel filled via collaterals will be compressed by hematoma. Manageability of the guidewire tip is of a great importance, therefore we consider the optimal guidewire pair in this case to be Shinobi plus and Gaia Second (Third) or two Shinobi plus guidewires.

The intravascular ultrasound to search for the true lumen in antegrade recanalization is a well-known option but infrequently used in practice because it requires, on the one hand, high skills for confident tissues differentiation, and, on the other, the possibility to advance the ultrasonic probe without damaging the vascular wall integrity. Under these conditions, IVUS significantly simplifies the lumen search and successful recanalization (Fig. 2).

The time point to terminate the recanalization attempts remains controversy. Although prolonged fluoroscopy and significant amount of used contrast media are natural limitations, the absolute values of these parameters can

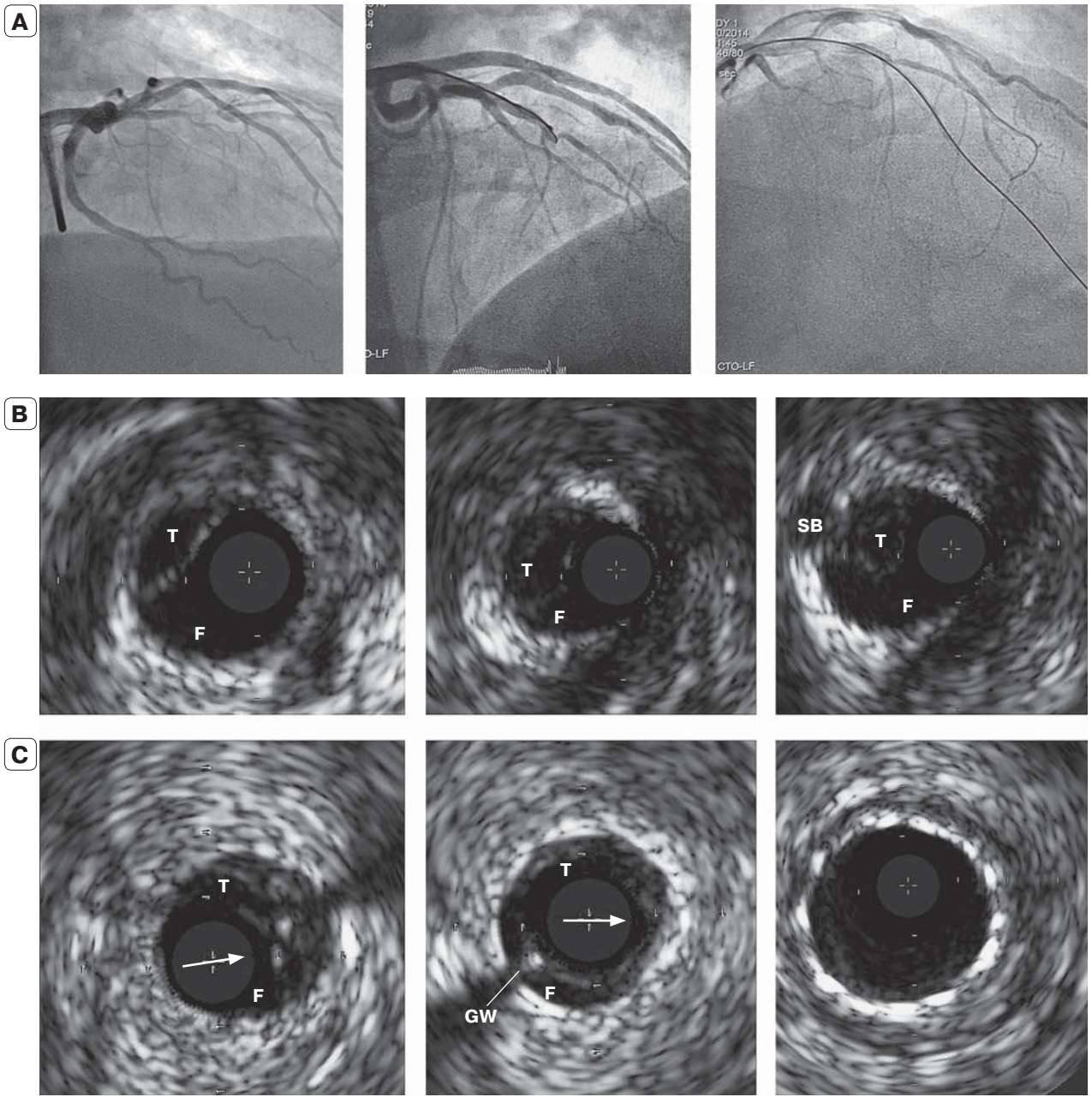

Figure 2. Clinical example of IVUS-guided recanalization.
A – baseline angiography. Type 1 segmental occlusion with good intra-system collaterals. However, the attempt to move the balloon through after recanalization using a coronary guidewire was unsuccessful.
B – ultrasound catheter was positioned in occlusion area. The probe is located in the false lumen, the true lumen is collapsed.
C – under IVUS guidance, the second guidewire was introduced in the true lumen, then the probe was introduced over this guidewire, its correct position in the lumen was confirmed. On right: post-stenting IVUS control.
D – follow-up angiography after stenting, complete restoration of blood flow.
T – true lumen, F – false lumen, GW – guidewire, SB – septal branch.

Possibility for correct selection of stent parameters

	Pre-interventional assessment	Post-recanalization assessment based on angiography data	Post-recanalization assessment based on IVUS data
Stent length:			
Type 1 occlusion	+	+	+
Type 2	±	±	+
Type 3	–	+	+
Diameter:			
If diameters differ	±	±	+
If reference segments are affected	–	±	+
Bifurcation	–	±	+

+ reliable estimate possible; ± incomplete or unreliable estimate; – estimate impossible.

be quite different. We consider the limiting parameters are as follows: fluoroscopy time – 60 min and amount of contrast – 500 mL. However, in some cases, futility of attempts may become apparent much earlier. Therefore, we consider very relevant the Professor D.G. Iosseliani's statement that during the intervention an experienced operator actually feels whether he/she will be able eventually to overcome an occlusion and it should direct his/her actions. The undisputed reason to terminate the intervention is pronounced subintimal or paravasal leakages.

In some cases, if primary recanalization fails, the attempts for re-intervention are justified. We consider them reasonable if there still are techniques unused in the primary intervention. Re-intervention should not be surely limited to repeating the previous techniques and should have a detailed plan starting with the peculiarities of catheterization and access (retrograde or antegrade) and ending with the selection of guidewire, method of its support and choice of balloon for initial crossing the occlusion. In our opinion, the optimum time for reattempt is 1.5–2 months after failed intervention. In some cases, the second intervention is facilitated by appearance of new channels and connections after the previous intervention. In our experience, retrograde recanalization is primarily used for re-interventions. For this purpose we almost always use Fielder XT guidewire and Corsair microcatheter (Asahi Intecc).

In some cases, the guidewire crossing does not mean successful recanalization as sometimes it is extremely difficult to introduce a coronary balloon. Rotablator seems very promising but requires the guidewire replacement with a special wire for this device; however, this is not always possible. Although special recanalization balloons are listed in the catalogs of many manufacturers, not all of them are really such balloons. We prefer to use for recanalization the following balloons: Emerge and Apex (push), Boston Scientific, and Tazuno, Terumo. In special cases, we use ultra low-profile balloons of 1.1 mm in diameter – Across CTO (Acrostak) and NIC 1.1 ULP CTO (SIS Medical) and even of 0.85 mm in diameter – NIC Nano 0.85 CTO (SIS Medical). A very useful technique is to screw the balloon counterclockwise and then clockwise (equal number of times) with a slight forward impact. This technique is effective in 9 of 10 difficult cases. Another specialized device – Tornus (Asahi Intecc), a microcatheter with a left-handed thread designed for "screwing" into a hard occlusion, is used in the remaining cases (10%). If these two techniques are ineffective, you should ensure the correctness of the guidewire position, possibly it is not in the true lumen.

As noted above, the intervention for coronary chronic total occlusion is not completed with its recanalization. The correct selection of appropriate stent and its optimal implantation are equally important. If these factors are underestimated, especially after quite long intervention till implantation, all recanalization efforts may be futile. It is also important that the long-term clinical outcome does not depend on the method of coronary chronic total occlusion recanalization (8). The long-term outcome to a greater extent depends on adequate stenting after recanalization.

In contrast to stenting in stenosis, in most cases prior to recanalization the operator can not pre-determine sizes of the stent(s) to be implanted or has very incomplete information (Table). This is especially relevant for Type 3 occlusions when reference segments are involved and bifurcations are affected (the presence of a side branch can not be determined in type 3 occlusions).

After recanalization, the situation is also not completely clear in most cases. This circumstance is influenced by the fact that the distal circulation does not adequately open immediately after the antegrade blood flow restoration. Administered nitrates only partially manage the situation and in many cases, intravascular ultrasound scanning is the only way to correctly choose the required stent for it gives correct answers to all questions on stent sizing.

Results

We performed 1256 recanalizations of the coronary arteries for chronic total occlusion within the period from 1998 to June 2015 including 602 interventions (47.9%) for the last 4.5 years. 88.6% of the intervened patients were men with mean age of 55.36 ± 7.15 y.o. 69.8% of patients had a history of myocardial infarction. 16.2% of the intervened patients had diabetes mellitus.

Recanalizations amounted to 19.0% out of all elective coronary endovascular interventions which is consistent with the average published percentage 7–20% (7, 9–12). This suggests that the selection criteria for endovascular recanalization were not very strict, that is important for objective assessment of the obtained results.

The left anterior descending artery was recanalized in most cases (40.8%). The right coronary artery and circumflex artery were intervened in 36.1% and 21.4% of cases, respectively. The venous coronary bypass grafts were recanalized in 0.6% of cases.

In our experience, the incidences of type 1, 2, and 3 occlusions were 25%, 43.8%, and 31.2%, respectively. Thus, we could only presumably determine the required size of the stent or had no data on the lesion size in 75% of cases before intervention. Frequent intravascular visualization is the only correct way of such assessment. Intravascular ultrasound was used in 17.5% of the total number of recanalizations. The majority of procedures (55%) were performed after recanalization and predilation, i.e., focused on selection of optimal tools for stenting. Follow-up IVUS after stent implantation amounted to one-third of all IVUS procedures. Over the last 4 years, optical coherence tomography to comprehensively assess adequacy of stent implantation was used for monitoring at the final stage of intervention in 22% of cases.

It should be noted that despite the well-established principles and approaches to chronic total occlusion recanalization in our clinic, they are not immutable dogmas and it is interesting to analyze their transformation. One of the most important factors impacting the changed technical approaches is conversion to transradial access as the main one, which in turn influences the selection of tools and techniques.

Until 2012 inclusively we used only transfemoral access for recanalization. In 2013, 2014, and 2015, the transradial access was used in 9.4%, 63.8%, and 79.1% of interventions, respectively. At the same time, the second access for contralateral arterial catheterization became much more widespread. The second femoral artery was catheterized in 1.3% of interventions till 2012. In 2013, the second access was already used in 29.9% of cases (91.4% – femoral access); in 2014 – 43.8% (93.5% – radial access); in 2015 – 49.3% (100% – radial access). It is partly related to less traumatic effect associated with radial access.

The flip side of radial access is less stable position and weaker support of the guiding catheter. This, in turn, requires more frequent use of special techniques to stabilize the system and improve the support of the guidewire. The microcatheter to support the guidewire and balloon anchoring technique were used in 0.9% and 0.3% cases, respectively till 2012, inclusively. Over the last 2.5 years, the microcatheter and anchoring technique were used for this purpose 5 and 23 times more often (4.5% and 6.9%), respectively. As noted above, the Guidezilla guide extension catheter (Boston Scientific) has recently become a significant marketed option. In cases when it can be used (occlusion localized in the middle or distal segments of the artery, sufficient diameter of the proximal segment to maintain patency of side branches after introduction of the guide extension catheter), this tool reliably stabilizes the entire system, creates the optimal support for introduction of the guidewire and balloon, and, very significantly, more than halves the amount of injected contrast media.

On average, 1.15 coronary guidewires per intervention were used for recanalization. As noted above, we used coronary guidewires Shinobi and Shinobi plus (Cordis) in the vast majority of cases; they were applied in 73.4% of all interventions and amounted to 64.3% of all the guidewires used. However, these tools accounted for 75.3% of guidewires used till 2012; over the last 2.5 years, this proportion slightly decreased to 42%. On the one hand, it was the

manifestation of some changes in interventional technique associated with conversion to transradial access, on the other hand, it was a consequence of development of new special guidewires. In our opinion, Gaia (Asahi) guidewires are of the greatest importance because they actually provide new opportunities compared to other guidewires. Over the last two years, we have used them in 25.7% of cases. Within the same time period, the Pilot (Abbott) guidewires were used in 15.3% of cases, Whisper (Abbott) – in 9.6%, Fielder (Asahi) – in 6.9%, JET (Abbott) – in 4.6%, and Progress (Abbott) – in 2.7% of cases. It is noteworthy that with increased use of guidewires other than Shinobi, several different guidewires were used within a single intervention significantly more often compared to the previous period (up to 20%), meanwhile Shinobi as a additional guidewire was used in three of each four cases.

We rarely use retrograde access although consider it necessary in our arsenal both in terms of specific technical skills and availability of specific tools. The proportion of retrograde access in our clinic is only 1.6%. In the vast majority of cases, we use it as a second-line option when antegrade recanalization fails. Recanalization has been re-attempted more frequently in recent years and over the last three years it was performed in 45% of patients when the first attempt was unsuccessful. The second attempt was successful in 62.5% of these patients, and retrograde access was used in a half of these interventions.

The method of recanalization completion has been transformed over the years. Fifteen–seventeen years ago, we implanted the bare-metal stents in a half of cases and performed balloon angioplasty in another half of interventions. In the next decade, bare-metal and drug-eluting stents were implanted in 58.2% and 32.3% of cases, respectively, and balloon angioplasty only was performed in 9.4% of cases. Finally, over the last three years, the bare-metal stents were implanted after recanalization in 10.3% of patients only, drug-eluting stents were implanted in 86.1% of patients, and balloon angioplasty was performed in 3.6% of patients. The reason for balloon angioplasty was identification of significantly poor peripheral circulation or a small-diameter artery which could not be suspected prior to intervention. The drug-eluting balloons were used in some of these cases.

Mean number of stents per lesion was 1.44 and the long coronary stents (>28 mm) were preferable. Postdilation of the middle part of the stent using a balloon of larger diameter (taking into account the intensity of positive remodeling) is an obligatory technique. In case of inadequate stent apposition, suspected blood clots or plaque prolapsed through the stent struts, possible mechanical deformation or stent underexpansion, intravascular imaging is required and OCT is preferable compared to IVUS.

The mentioned technical principles, developed treatment strategy, as well as constant introduction of new tools and techniques into real practice while maintaining a balanced approach to their use let us achieve good results of chronic total occlusion recanalizations in our

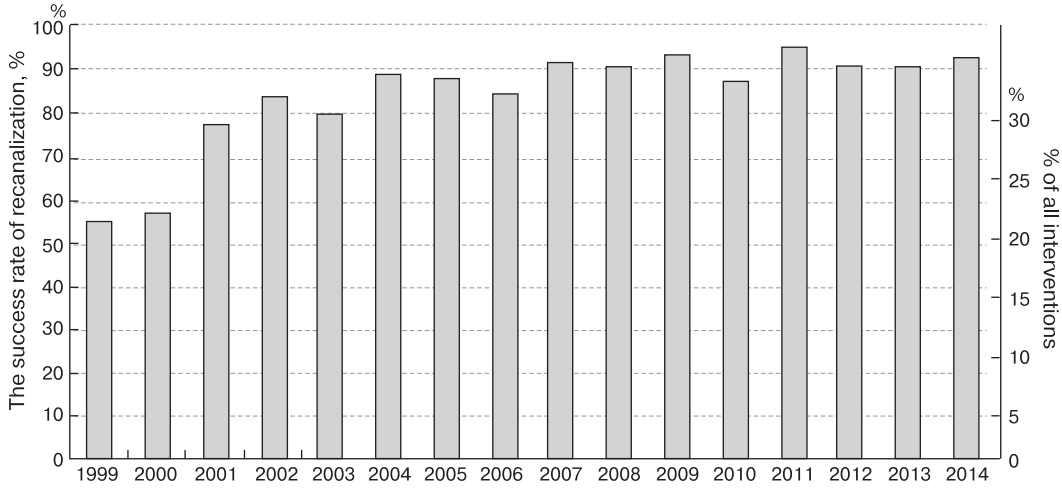

Figure 3. The success rate of chronic coronary occlusions recanalization. Grey columns – the success rate of recanalization, %; black line – percentage of recanalized chronic occlusions out of the total number of elective coronary interventions.

clinic. From 1999 to 2015, the immediate success rate of recanalization was 88.3% with fluctuations from 84.4% to 95.2% in the last 10 years. The average success rate was 92% within the period from 2011 to 2015. Another 0.5% should be added to these values after the above mentioned successful recanalization reattempts. As noted above, it is significant that these values are not associated with a strict selection of the patients. Figure 3 shows the success rate of recanalization per year and percentage of chronic total occlusion recanalizations of the total number of elective coronary interventions. As this Figure demonstrates, over the last 10 years the recanalization rate ranged from 15.5% to 23.6% of all coronary angioplasties (on average, 19%) which is even higher than the literature data.

Conclusion

Recanalization of coronary chronic total occlusion remains one of the most difficult and one of the most individualized endovascular interventions. The tried and tested technical approaches and algorithms, rational and differentiated application of various specialized tools help to achieve high success rate of recanalization even at low rates of retrograde access. Optimal stent sizing in recanalization of the chronic total occlusions of the coronary arteries is a creative process requiring the operator to be vigilant both during preparation for intervention and after recanalization. The intravascular imaging at different stages of intervention contributes to good long-term outcomes.

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20-year Experience with Intravascular Ultrasound Scanning in a Multidisciplinary Hospital

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Approximately 20-year experience with intravascular ultrasound in a multidisciplinary clinic was analyzed. 3624 intravascular ultrasounds were performed; that greatly exceeds the number of such procedures performed in any other department in the country. Coronary IVUS accounted for 83.7% out of the performed procedures, and the rest (16.3%) were IVUS procedures for other vessels including peripheral and renal vessels, abdominal aorta as well as procedures for congenital heart defects.

Key words: *intravascular ultrasound, coronary stenting, intravascular visualization.*

Objective. To analyze the technological development and clinical informative value of intravascular ultrasound scanning for diagnostic and treatment procedures in the various parts of the cardiovascular system.

Methods. From 1996 to 2015, inclusively, there were 6 IVUS devices of various manufacturers and 4 out of them (including two devices built into angiography systems) are currently used in the Department of Radiosurgical Techniques for Diagnostics and Treatment (RSTD&T) of Orenburg Regional Clinical Hospital. Existing IVUS devices can operate with both phase-electronic and mechanical probes, 2 of them also have units for measuring fractional flow reserve.

Results. Totally, 3624 intravascular ultrasounds of various vascular basins were performed, i.e.: 83.7% – coronary arteries (half of cases combined with RF analysis – "virtual histology" or iMAP), 8.4% - congenital pathology, 3.9% – aorta and renal arteries, 2.4% – lower limb arteries, 0.3% – other and rare procedures. Only two complications (0.06%), directly related to IVUS were observed throughout the reporting period.

Conclusions. Pre-interventional intravascular ultrasound provides the most accurate qualitative and quantitative information on the target lesion optimizing the course of the intervention, and post-interventional intravascular ultrasound objectively evaluates the intervention results. The widespread use of IVUS in clinical practice not only helps to solve diagnostic and tactical tasks, but also contributes to establishing by a clinician a responsible, balanced and objective approach to assessment of the lesion, selection of the tools, ultimately promoting the achievement of good treatment results, both immediate and long-term.

Introduction

Since its appearance, intravascular imaging has become one of the most striking reflections of the qualities that distinguish endovascular diagnostics and treatment methods in general, i.e., miniaturization, high technology, and efficacy. It is considered that the history of intravascular ultrasound which remains the most common intravascular visualization option, originated in 1989, and thus, this option celebrated its 25th anniversary in 2014. This was preceded by a "prehistory" period from 1971 to 1989, when N. Bom laid the foundations of the technologies that gave rise to the first clinical devices. It should be noted that despite technological advantages the IVUS probes have remained fundamentally unchanged till present. Moreover, the previous articles have already foreseen almost all ways of subsequent technological development of the systems including priority use for stenting, creation of hybrid probes and techniques, development of intravascular Doppler and flowmetry, synthe-

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sis of 3D image based on intravascular ultrasound data (1–4).

Of course, as for majority of intravascular options, fundamental for IVUS is its relevance in diagnostics and treatment of coronary arteries as the most extensive and highly expensive section of interventional care. There is a quite clear link between the development of interventional therapies and intravascular imaging options. The appearance of stents marked the second revolution in interventional cardiology after introduction of balloon angioplasty. Namely intravascular ultrasound contributed to development and introduction of the concept of optimal stent expansion as one of the most important conditions for favorable immediate and long-term outcome. For many years, IVUS was the "gold standard" for difficult cases both in daily practice and, primarily, scientific research.

After development of drug-eluting stents which marked the third revolution in interventional cardiology, IVUS, in the opinion of some authors, became unnecessary to achieve good clinical outcomes. However, appearance of a number of challenges specific to drug-eluting stents quite quickly forced not only to return to idea of accurate visual monitoring of the adequacy of stent implantation but also contributed to IVUS popularity. Moreover, at this stage, another method of intravascular imaging appeared that rapidly developed and now is comparable with intravascular ultrasound – optical coherence tomography. At this stage, the growth in fractional flow reserve investigations should be noted; the method appeared quite long ago but proved its value and completely developed only in the last decade.

Finally, the fourth revolution in interventional cardiology is considered to be the clinical introduction of bioabsorbable implants – scaffolds. Considering the design of this type of stents and technology of their implantation, accurate sizing and quality control of their implantation play a major role. Intravascular imaging options in this respect are absolutely indispensable and OCT as an option providing detailed information on the intraluminal structures has a dominant value.

Although coronary procedures are clearly predominant, the significance of intravascular imaging options is not limited to them. While there are much less procedures for other vascular basins, IVUS and OCT are used in the peripheral, renal, brachiocephalic arteries, and some types of congenital abnormalities.

The first national publications on intravascular ultrasound for diagnostics of lower limb arteries concern the non-coronary IVUS options (5–7). Ivanitskiy A.V. et al. (8–10) have demonstrated the potential of this option for diagnostics of pulmonary arteries pathology. First national publications concerning IVUS in coronary pathology were published in 1995–1996 (11, 12). All these publications analyzed experience with IVUS mechanical probes. Clinical trials were conducted and the IVUS device with phase-electronic probes was subsequently introduced into the national practice in our clinic, which was reflected in some publications including monographs (13–18).

Materials and methods

The first intravascular ultrasounds in the Department of Endovascular Methods of Diagnosis and Treatment of Orenburg Regional Clinical Hospital were performed in 1996 when the clinical trials of Oracle, EndoSonics were conducted at our site. It should be noted that the Department started working to the full also in 1996. Thus, IVUS is the same age as our Department. In fact, our listing of devices and catheters used represents a history of this option improvement.

The complex catheters Oracle F/x Plus, Oracle, Focus F/x and Oracle Megasonics F/x combined with angioplasty catheters were already used in an early version of the device along with the simple diagnostic phase-electronic probes Visions F/x, 20 MHz. The procedure in this device was recorded on a video tape only, hence processing and subsequent analysis were limited.

Further development of this device led to appearance of Oracle In-Vision, subsequently modified to In-Vision Plus complex (which used In-Vision Gold software already appeared under the name of Jomed). This complex was already fully digital device compatible with the DICOM and able of CD recording. Moreover, new functions and capabilities appeared: reconstruction of the third projection to measure accurately the lesion length and choose optimally the stent if automated pullback system is used, and Chroma Flo enabling to better identify the lumen via color mapping of blood flow. A new generation of probes was already incompatible with previous devices, although their line expanded: in addition to Vision Five-64 F/x and Megasonics Five-64 F/x which continued the previous series, the new versions of the probes Visions PV 018 F/x (slightly larger pro-

file with greater depth of penetration) and Visions PV 8.2 F (frequency of 10 MHz, 8.2 F profile, potentially able to examine large vessels up to the aorta and heart chambers) appeared. In our opinion, experience with JoSonics Flex based on the principle "three in one" was very interesting and clinically justified: stent mounted on the balloon combined with an ultrasonic probe. Unfortunately, this type of probes was manufactured for a relatively short time and then balloons combined with the ultrasound probe were also discontinued. Coronary probes were evolutionary improved and a new model – Avanar F/x without fundamental changes in properties and image quality was developed.

S5 complex manufactured under a new brand of Volcano became the next generation of the phase-electronic probes. This device was the first equipped with the version integrated into an angiographic complex. When replacing the existing angiography systems and after the end of In-Vision Plus service life three S5 devices were sequentially put into operation in our Department: one – mobile version and two – integrated in angiography systems (S5i). The main fundamental difference to the previously existing device was the function of IVUS radiofrequency data analysis – "virtual histology" (first introduced by the manufacturer in the IVG3). The device is compatible with previous versions of the probes along with a new generation – Eagle Eye, Eagle Eye Gold, and Eagle Eye Platinum. Moreover, a new step made by the manufacturer for greater satisfaction of the users' requests was the possibility to use both phase-electronic and mechanical high-frequency probes on a single platform (Revolution, 45 MHz).

We also use another device that represents the most recent generation of another branch of currently available IVUS devices – iLab, Boston Scientific. The program base of the device has been improved for several years. One of the features of the current version is a type of radiofrequency analysis – iMap, which, however, may disappear in the new version of the program. The current generation are coronary (Atlantis SR Pro 40 MHz) and intracardiac (Ultra ICE, 9 MHz) probes.

Out of four IVUS devices placed in three X-ray operating rooms, there are two integrated and two mobile versions. All systems display information on a monitor suspended in the operating room, making information acquisition and processing more convenient. Such a deployment of devices makes it possible to perform intravascular ultrasound of any vessel at any time in each operating room.

Results

The settings of a multidisciplinary hospital in which our Department works, dictate the need to perform endovascular interventions on different parts of the vascular system. A natural consequence is the desire to apply available modern diagnostic tools not only in the coronary procedures but also for other parts of the cardiovascular system.

Intravascular ultrasound has become an integral part of the clinical work of the Department and is routinely used. Totally, from 1996 to 2015 inclusively, 3624 intravascular ultrasounds were performed in our Department that greatly exceeds the experience of any other Department in the country.

As Figure 1 shows, throughout the reported period the annual number of IVUS significantly varied and we can distinguish several periods accordingly: first five years (1996–2000): 50 per year (12–46), 2001–2008: ranged from 50 to 100 per year, next three years: increased on average up to 150 per year with the growth of the total number of coronary interventions, and 2012–2014 (when the randomized trial Orenburg (19) was conducted): substantially exceeded 600 per year.

Of course, the vast majority of procedures (3081 – 83.7%) were performed in coronary arteries for coronary heart disease (Table). The number of IVUS primarily increased due to coronary procedures (Fig. 2). However, the number of non-coronary IVUS procedures (16.3%) exceeds the experience of most Russian clinics possessing appropriate equipment. Interestingly, within the first years of this option mastering, the numbers of IVUS in coronary arteries and all other vascular localizations were comparable.

We have previously analyzed various aspects of clinical application of IVUS in coronary interventions (17, 20). It should be emphasized that this option used routinely does not imply its application in most interventions which is confirmed by the completed trials. A differentiated case-specific approach to IVUS should be followed. The experience of the operator in this case is crucial, firstly, to make a decision on IVUS appropriateness in each specific case, and secondly, to perform procedure safely and quickly without significant prolongation of intervention. However, in our opinion, IVUS is almost mandatory in a number of cases. These

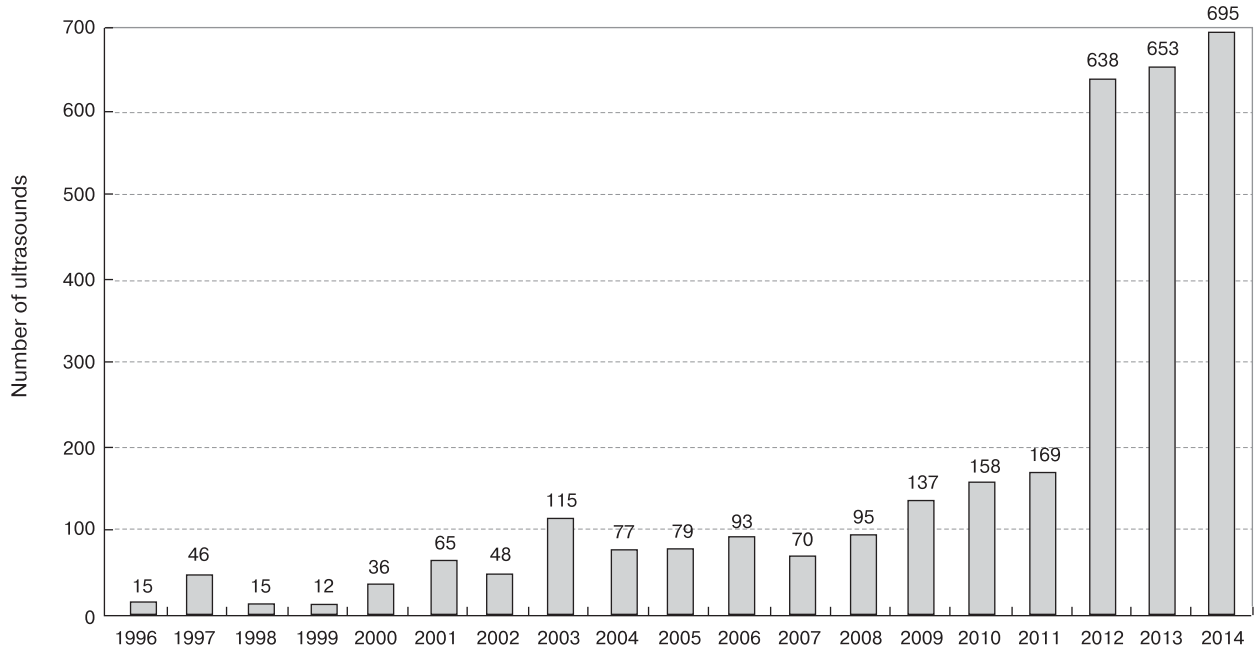

Figure 1. The number of IVUS performed in Orenburg Regional Clinical Hospital (by year).

IVUS procedures in various vessels throughout the reporting period

	Coronary arteries	Congenital abnormalities		Peripheral arteries					Rare cases	TOTAL
		PAD	Aortic coarctation	Renal arteries	Aorta	Iliac arteries	Femoral arteries	Popliteal arteries		
N	3081	274	29	119	23	39	44	4	11	3624
%	83,7	7.6	0.8	3.3	0.6	1.1	1.2	0.1	0.3	100

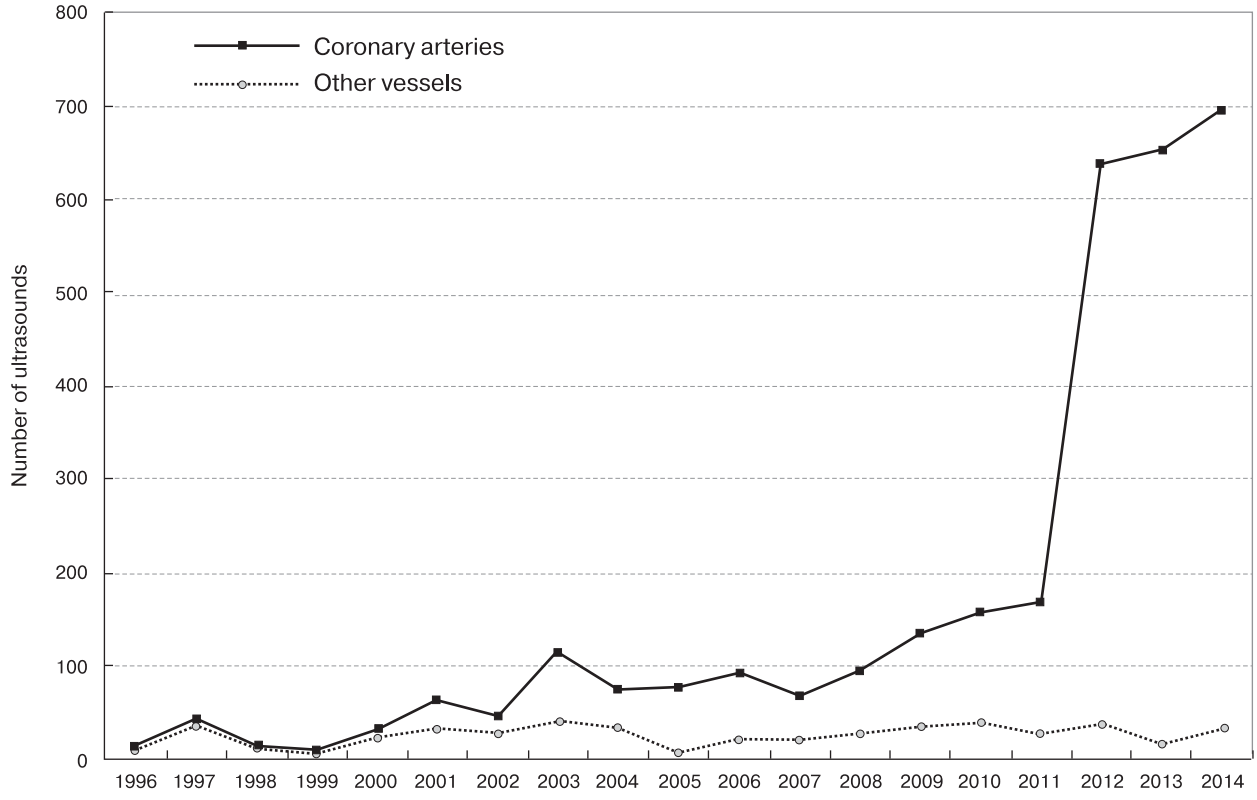

Figure 2. Ratio of intravascular ultrasounds of various vessels per year.

include, in particular, left main coronary artery stenting, implantation of special bifurcation stents or bioabsorbable scaffolds. In these cases, IVUS (or, sometimes, OCT) is mandatory in our clinic. IVUS used at the initial stage of the intervention (sometimes already at the diagnostics stage) gives precise morphological parameters of the vessel in order to choose the tools of optimal size. Intra-interventional control procedures assess the adequacy of the performed steps and help to decide whether to continue / complete the intervention and what measures should be taken. If target parameters are not achieved, an additional impact is performed using larger balloon, higher pressure or more prolonged exposure depending on the obtained parameters. At the final stage, adequacy of the performed intervention can be assessed immediately at the operating table according to our own criteria (17, 20). The main objective of IVUS is to optimize clinical outcomes, including the restenosis rate.

IVUS with analysis of the backscattered RF signal ("virtual histology" or iMAP), performed in more than a half of all coronary procedures (1648 cases) greatly supplemented the gray-scale intravascular ultrasound findings at the initial stage of the intervention and helped to distinguish the histological structure of atheroma and identify necrotic, calcified, fibrous and lipid tissues. In some cases, we considered the RF analysis data when deciding on feasibility of intervention for "borderline" lesions – intervention for histologically unstable areas or no intervention if signs of instability were absent.

The advantage of IVUS compared to a new option of intravascular diagnostics – optical coherence tomography (OCT) is a great penetrating ability of ultrasound permitting to assess the entire thickness of the vascular wall and stenosing substrate, while OCT provides more detailed and reliable information on intraluminal masses, stent status, and intima. Therefore, with a certain degree of simplification, it is possible to say about priority use of intravascular ultrasound at the initial stages of the intervention and optical coherence tomography as a quality control at final stages.

In addition to the coronary arteries, we follow routine approach to intravascular ultrasound in two populations.

We perform the majority (67.6%) of renal interventions under IVUS guidance starting from the early period when interventions were performed without stenting. It is anatomically justified: due to significant difference between angiographic and ultrasound measurements of the renal artery diameters, angiography does not provide correct reference diameters in some cases of ostial lesions. In our experience, the average reference arterial diameter at the stenting area by IVUS was 0.64–1.0 mm larger than angiographic measurements, so a stent of different diameter should be chosen (17, 21, 22). Clinical results confirm the feasibility of this approach; we have only single cases of in-stent restenosis in the renal arteries.

In our experience, the measurements of patent ductus arteriosus take the first place among non-coronary IVUS (7.6% of all IVUS and 56.3% of all PDA closure interventions). Accurate measurement of the arterial duct and its ampulla using IVUS provides the opportunity to adequately choose the size and type of the tool for duct closure (23, 24). The variants and features of morphological structure of the duct first described by us are of practical interest and ultimately affect the safety and outcome of the intervention (17).

IVUS was also informative for another type of congenital abnormalities – aortic coarctation (17, 24). We performed 29 such procedures. Given the greater measurement precision compared to angiography, the option potentially facilitates choosing a size of balloon for aortic angioplasty or implanted stent. However, the measurement of the reference diameter at the coarctation level is impossible due to the nature of this pathology, and measurement of the reference diameter at the diaphragm level (as in the analysis of angiographic data) slightly minimizes the difference of the results.

IVUS of the atherosclerotic lower limb arteries and aorta was performed in 110 cases, out of which aortic IVUS was performed in 23 cases, superficial and deep femoral arteries were diagnosed in 44 cases, iliac and popliteal arteries in 39 and 4 cases, respectively. The method is a priority for angiographically uncertain, eccentric and prolonged peripheral vascular lesions. As mentioned above, we used IVUS in peripheral arteries more frequently at the stage of experience accumulation. However, currently it is mandatory manner in some cases. One of these indications is the necessity for stenting of the atherosclerotic terminal aorta with or without involvement of the iliac arteries (17). Moreover, intravascular ultrasound is highly advisable after mechanical recanalization, drug-eluting balloons, for borderlines restenosis in peripheral stents.

IVUS can be successful in a number of other non-standard clinical cases providing the necessary diagnostic information for optimal treatment as evidenced by some rare cases when we used it for interventions on coronary bypass grafts (4 patients), arteriovenous fistulas (2 patients), venous vessels (5 patients), and others (17).

The safety issues of the option need special considerations. Only two complications (0.06%) directly related to IVUS were observed throughout the reporting period. If the technology is followed, coagulation system (activated clotting time monitoring, supplemental heparin therapy when this option is used at the diagnostic stage) is controlled, there is certain experience and ability to quickly assess the results at the operating table, intravascular ultrasound is a safe and highly informative modern invasive diagnostics option. Only 7–12 minutes depending on the number of catheter pullbacks are required additionally; meanwhile, the operator gets incommensurable clinical advantages.

Conclusion

Angiography considered the "gold standard" for a long time gives information on the vascular lumen, but not its structure. By providing this information IVUS contributed to achievement of modern level of coronary angioplasty and stenting. IVUS was introduced into practice ten years later than coronary angioplasty, but played a huge role in development of modern strategies of interventions. It is based on the most modern catheter, electronic and computer technologies and provides the most accurate information on the degree and extent of lesion and characteristics of atheromatous plaque to optimize the stent selection pre-interventionally and assesses the adequacy of implantation post-interventionally. The widespread use of IVUS in clinical practice not only helps to solve diagnostic and tactical tasks, but also contributes to establishing by a clinician a responsible, balanced and objective approach to assessment of the lesion, selection of the tools, ultimately promoting the achievement of good treatment results, both immediate and long-term.

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Optimal Implantation of Dedicated Bifurcation Stents for the Treatment of Coronary Bifurcation Lesions Using Intravascular Imaging: a 10-year Experience

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The treatment of coronary bifurcation lesions remains a thrilling problem of interventional cardiology. We present our experience with the treatment of this pathology using dedicated bifurcation stents, implanted under intravascular imaging control. 164 dedicated bifurcation stents of 7 types were implanted in 158 patients. 146 procedures were performed under IVUS, 9 – under OCT control. The rate of restenosis was 11.6%, with the use of DES – 4.7%. The rate of restenosis after the IVUS-controlled procedures was 8.9%, under angiographic control – 33.3%. According to the data of control angiography and telephone survey, within 8 years after the procedure the positive effect was preserved in 81% of cases.

Keywords: *bifurcation lesion, coronary stenting, dedicated bifurcation stents, intravascular imaging, intravascular ultrasound, optical coherence tomography.*

Methods. 164 dedicated bifurcation stents of 7 different types were implanted in 158 patients. The "true" bifurcations (types 1,1,1, 1,0,1 and 0,1,1) were found in 64.6% of cases. In 146 cases (89.0%) IVUS-assisted procedures were performed. In 9 cases the procedures of bifurcation stenting were performed under the control of optical coherence tomography.

Results. Technical success after the implantation of dedicated bifurcation stents was noted in 100%. All patients had favorable immediate clinical results. There was 1 case of side branch thrombosis at day 2 after the procedure. The rate of restenosis was 11.6%: 4.7% in the group with DES and 19.2% in the group with BMS. The rate of restenosis in the "true" bifurcation subgroup was 17.9%, in the remaining subgroups – 8.3%. The rate of resetnosis after the procedures performed under IVUS control was significantly lower than with the use of angiographic control only – 8.9% and 33.3%, respectively. Control coronary angiography was performed for clinical indications in 36 patients within 2 months – 8 years after the procedure, 18 in-stent restenosis were found. Another 64 patients answered to telephone survey, 63 of them noted an improvement or a stable condition. In total, within 8 years after the procedure, positive results were preserved in 81% of cases.

Conclusions. The use of dedicated bifurcation stents is an effective method for the treatment of coronary bifurcation lesions. The use of intravascular ultrasound and optical coherence tomography allows to optimize the choice of stent, the results of implantation and the long-term results of treatment.

Introduction

Bifurcation lesions are an everyday finding in the clinical practice of interventional cardiologists who face them in about 15–20% of all cases of percutaneous coronary interventions (1, 2).

According to the data of numerous randomized trials and registries, most experts, including the Consensus from the European Bifurcation Club (EBC), consider it preferably to treat bifurcation lesions with one stent, with provisional use of the second stent only in cases with marked restenosis or limited patency of the side branch after the stenting of the main branch (2). In the meantime, the document of the European Bifurcation Club states, that the above trials often included not "true" bifurcations or the lesions with side branch diameter < 2,5 mm. However, several trials (Nordic-Balti

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cIV trial, DKCRUSH II trial) have demonstrated a trend towards better results with two-stents approach in cases with side branch diameter > 2.75 mm and side branch stenosis > 50%. For this reason, the Consensus from EBS suggests the use of two-stent strategy in the presence of a large side branch and its extended lesion (2). This can be supplemented by an unfavorable re-crossing angle after the stenting of the main branch, as well as the adjustments for the side branch diameter (> 2,5 mm) and the extension of its lesion from the ostium – over 10 mm (3).

One should also consider important technical limitation connected with the use of a customary approach to the angioplasty of the bifurcation lesions: the problems related to the maintenance of side branch access during the procedure; the compression of the side branch by the struts of the stent implanted to the main branch, which makes it difficult to re-insert the guidewire or to advance the balloon/stent into the side branch; the deformation of the main branch during the dilatation of the side branch; the unfeasibility of complete coverage and reinforcement of the side branch ostium; the impossibility to preserve the stent structure and its deformation during balloon angioplasty of the side branch (4, 5). In addition, the insufficient informative value of angiography for a reliable evaluation of the results of bifurcation stenting increases the possibility of obtaining suboptimal results, that will become clinically evident in the long-term.

One of the ways for the solution of these problems are dedicated bifurcation stents – ideally, they should be free of the above shortcomings. In the same time, the task of creating an optimal bifurcation stent still can not be considered solved. The weak points of the commercial stents are a rather high profile hindering the manipulations, somewhat complicated methods of delivery and positioning in relation to the side branch, still limited range of size, mainly in what concerns the length. However the search of an optimal bifurcation platform goes on, and the spectrum of suggested stents is increasing, while not as fast, as several years ago. Certain tactical problems related to the use of dedicated bifurcation stents still are not solved: in which cases is it preferable to use them; which bifurcation design should be used in the given situation; which long-term results can be obtained with the use of these devices. Probably, the uncertainty with these problems can explain the low interest towards the use of dedicated bifurcation stents in Russia.

The advantage of dedicated bifurcation stents consists in a certain unification of the provisional one-stent and multi-stent strategies in the same device. Their use results in a more reliable control of the sided branch patency during the procedure, in most cases – without necessary re-advancing of the guidewire; othe size of the stent mesh at the level of the side branch is more adequate, without destruction or marked deformation of the stent structure (which, in case of DES, is associated with the damage of the coating); there are no problems associated with balloon advancement for final kissing; such type of stents can be considered preferable in the presence of Medina 0,0,1 lesions, when the plaque is located only in the ostium of a large side branch and other strategies are associated with the risk of compromising the intact main branch (6). The Consensus from the European Bifircation Club states that the indications for the use of dedicated bifurcation systems are limited, however they can be useful in cases when the two-stent strategy seems optimal (2).

Despite the existence of several classifications of dedicated bifurcation stents, for clinical use it is enough to distinguish three main groups (5, 7). The first group consists of stents for provisional side branch stenting, which facilitate or support the access to the side branch after the stenting of the main branch and do not require re-crossing of the stent in the main branch. This group comprises the majority of stents, presently available at Russian market (Fig. 1). Most stents in this group have a particular feature – the formation of the carina in the area of the side branch ostium, which in many cases is enough for more solid fixation of the plaque in the ostium. In cases, when it is necessary to stent the side branch, it can be performed in the most anatomical fashion, without stent deformation in the main artery and with good ostial coverage. In our opinion, the most successful stent in this group is Everolimus-eluting Xience SBA with cobalt-chromium platform, whose design is mainly the same as this one of the well-acclaimed Multi-Link Frontier stent (8). Unfortunately, the production of this stent was stopped. A cobalt-chromium stent NileCroCo also has a drug-eluting variant NilePax (9), however Paclitaxel is not so effective. An interesting alternative for such kind of stents is Petal (Boston Scientific), with an original “sleeve” protecting the whole circumference of the side branch ostium (10). Unhappily, up to now this stent is

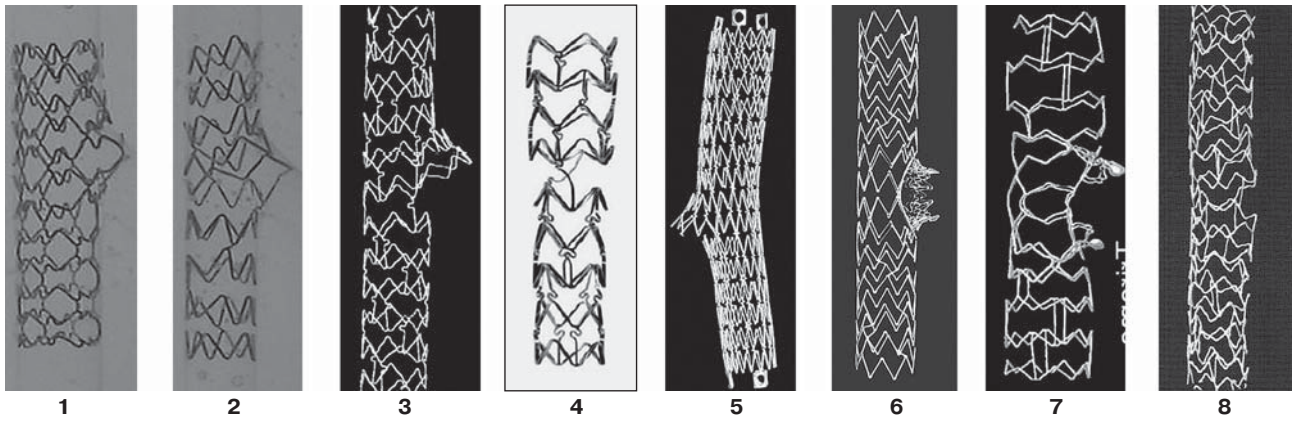


Figure 1. Stents for provisional stenting of the side branch. Available in Russia: Twin-Rail (1), Nile Pax and Nile CroCo (2), Xience SBA and Multi-Link Frontier (3), BiOSS (4); Coming into the Russian market – Stentys (5); Not registered in Russia or not used in clinical practice– Petal (6), Antares (7), SideKick (8).

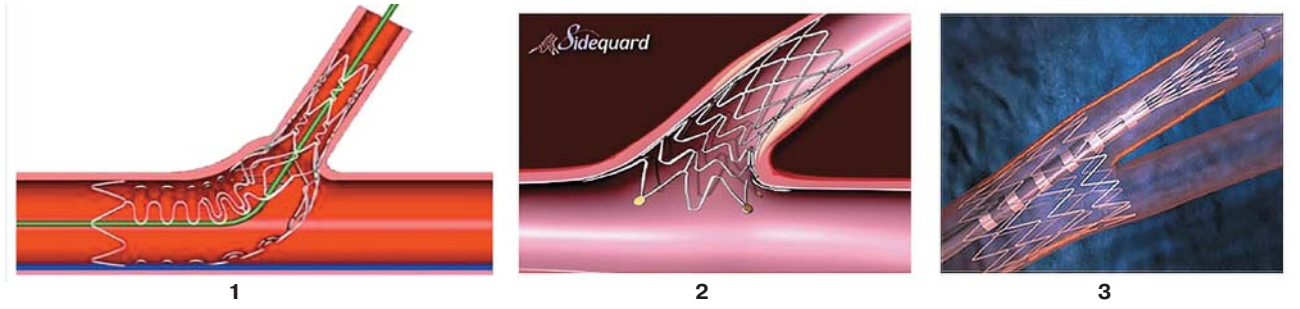


Figure 2. Stents generally requiring the implantation of additional stent(s) into thwe bifurcation. Side-branch stents – Tryton (1), Cappella Sideguard (2); proximal bifurcation stent – Axxess.

not yet used in clinical practice. The conception of BiOSS stent, with Sirollimus- or Paclitaxel-eluting and bare metal options, is based on the maximal adaptation to the vessel's anatomy due to the difference in the diameters of the proximal and distal segments. With this, the meshes in the middle segments are maximally wide for the access to the side branch, but this can be a problem in the presence of a big plaque mass in this area. This stent is being increasingly used in clinical practice and gets a good research basis (11–13). Finally, we consider as very interesting the conception of a self-deploying stent Stentys, which will gain the Russian market in the nearest future. Besides good apposition to the vessel's walls, this stent, after being implanted, allows to advance the guidewire in any site and to create a carina without deformation of the stent structure. According to several authors, this stent demonstrates good results, including in the management of acute myocardial infarction (14, 15).

The second group comprises the devices, which usually necessitates additional stent(s) implantation into the bifurcation (Fig. 2). The most widely spread among them is Tryton, with a rather large evidence base of successful use (16–18).

The third group consists of the "true: bifurcations tents (Y-stents, Fig. 3). In fact, these stents represent two joined enfografts, which optimally cover the main as well as the side branch. Despite positive results, the bulkiness of the available systems and their limited deliverability, still hinder their widespread practical introduction (19–20).

Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) can provide key information during the management of bifurcation lesions, and these data are superior to those of angiography. Both techniques can be used for the evaluation of the structure and the extension of the lesion, the results of predilatation, reference dimensions of the vessel (21–22). After stenting both techniques can be used for the evaluation of the adequacy of vessel's dilatation and of the deformation of the stent, as well as for the search of malapposition. The value of intracoronary imaging is re-

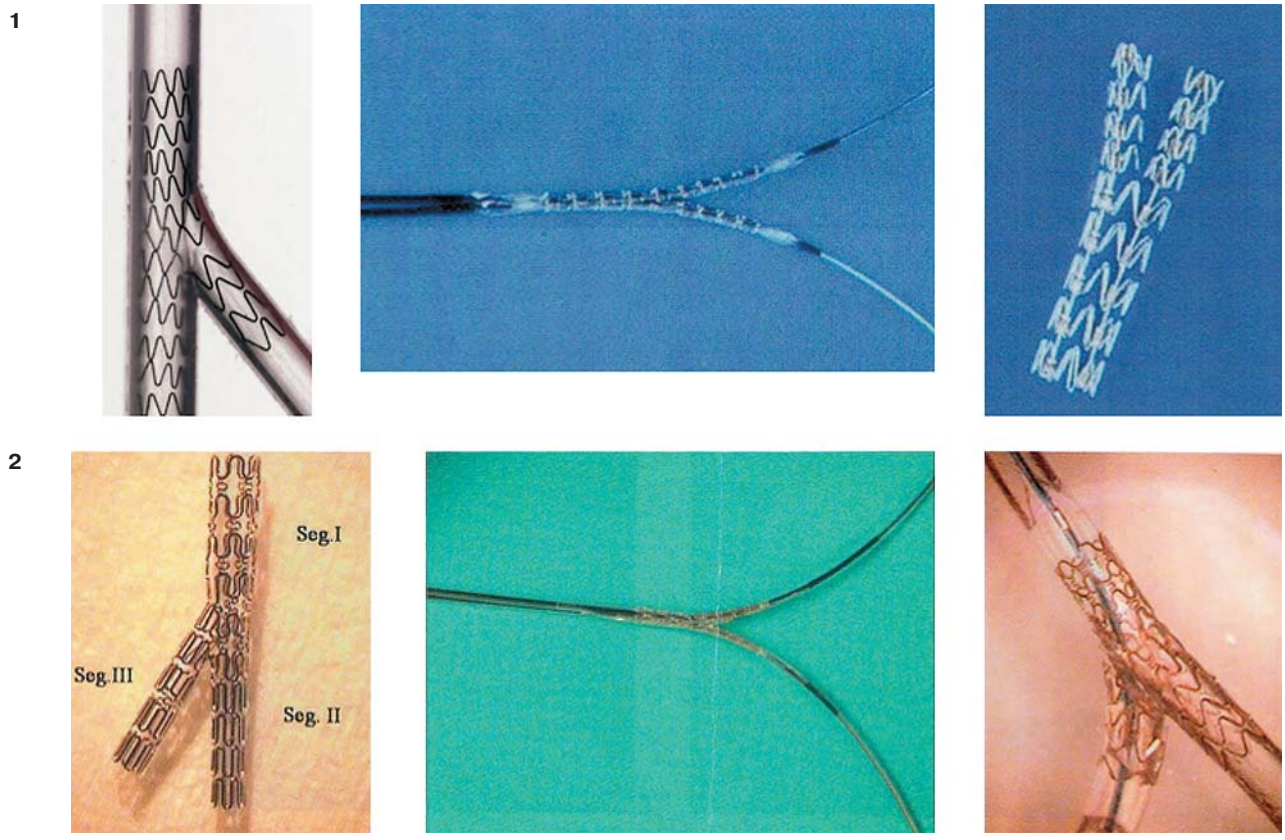


Figure 3. "True" bifurcation stents (Y-stents): Medtronic Bifurcation Stent System (1), DBS stent (Cordis) (2).

flected in the Consensus from the EBC (2). It is important, that an additional level of information can be obtained by the construction of a third projection of an intravascular ultrasound image (5), especially – 3D reconstruction of OCT data (23,34). With the use of dedicated bifurcation stents the significance of intravascular imaging techniques is manifold increased in comparison with single-stent management of bifurcation lesions.

Material and methods

From 2004 through August, 2015, 164 dedicated bifurcation stents were implanted in 158 patients. In 157 cases the procedures were elective, one bifurcation stent was implanted on emergency basis. We have used 7 types of dedicated bifurcation stents: 51 stents NilePAX (31.1%), 30 stents BIOSSLim (18.3%), 28 stents Multi-Link Frontier(17.1%), 25 stents Tryton (15.2%), 16 stents NileCroCo (9.8%), 9 stents -Rail (5.5%), 5 stents Xience SBA (3%). Herewith, the stents Multi-Link Frontier and Xience SBA were used clinically for the first time in Russia just in our department. The majority of our patients were males – 137 (87%). The age distribution was as follows: 30–39 years – 3 patients (1.9%), 40–49 years – 22 (13.9%), 50–59 years – 77 (48.8%), 60–69 years – 41 (25.9%), 70–79 years – 15 patients (9.5%). Hence, the average age of our patients was 57.3 ± 6.47 years. The ischemic heart disease (IHD) was associated with arterial hypertension in 89.1% of patients, hypercholesterolemia was revealed in 74.4% of cases, diabetes mellitus was present in 10.1%, and 60.5% of patients had postinfarction cardiosclerosis. 95 patients (57.9%) had bifurcation lesions in the left anterior descending artery (LAD) and the diagonal branch (DB), 41 (25.0%) – in the circumflex artery (CxA) and the obtuse margin branch (OMB), 16 (9.8%) – in the right coronary artery (RCA), 11 (6.7%) – in the left main coronary artery, and 1 patient (0.6%) had lesion in the intermediate branch. Herewith, the dedicated bifurcation stents allowed to correct the lesions in two bifurcations (LAD-DB, CxA-OMB) in 4 patients, and in 3 bifurcations (KAD-DB, CxA-OMB, RCA) in one patient. Other coronary lesions were corrected in 88 patients (51.9%), in 17 of them – simultaneously with the correction of bifurcation stenosis (10.8%).

According to Medina classification, the bifurcation lesions were distributed as follows: type 1,1,1 – 64 (39.0%); type 0,1,1 – 30 (18.3%); type 0,1,0 – 26 (15.9%); type 1,1,0 – 22 (13.4%);

type 1,0,1 – 12 (7.3%); type 1,0,0 – 9 (5.5%), and type 0,0,1 – 1 (0.6%). Thus, the so-called "true" bifurcations (types 1,1,1; 1,0,1 and 0,1,1) were present in 64.6% of all cases.

From 164 arteries operated with the use of bifurcation stents, intravascular ultrasound imaging was used in 146 cases (89.0%). IVUS was not used in cases, when the procedure was accompanied by technical problems necessitating the limitation of the duration of intervention or complicating the insertion of the transducer. IVUS was carried out with various devices available in our department: OracleIn-Vision (EndoSonics / Jomed / Abbott), s5и s5i (Volcano), with the use of phased-electronic transducers Jovus Avanar F/x, Visions PV.018, Eagle Eye, Eagle Eye Gold, Eagle Eye Platinum; and iLab (Boston Scientific), using mechanical transducers AtlantisPro. With the account of relatively small length of the lesions, subjected to bifurcation stenting in view of limited length of dedicated stents, the determination of the lesion's length was not a priority task of IVUS. For this reason we have used not mechanical, but manual pullback devices (except for mechanical iLab transducers).

Optical coherence tomography was used for the control during 9 procedures of bifurcation stenting in 8 patients. OCT was performed using C7-XR/Ilumien (LightLab / St. Jude Medical) device with C7 Dragonfly transducer and Lunawave (Terumo) with FastView transducer. Only mechanical high-speed (20 to 40 mm/sec) pullback devices were used. In 2 cases OCT was use at the initial stage of the procedure, and in 7 cases – at the final stage. At the initial stage OCT was applied in cases, when we wanted to evaluate simultaneously the state of the lumen in earlier implanted stents in order to understand, if the plasty with drug-eluting balloons was necessary. In 2 cases control OCT revealed edge stent-related problems – malapposition and intima dissection – which necessitated additional plasty with non-compliant larger balloon and implantation of an additional stent, respectively. Obviously, the use of OCT has a big potential in terms of eventual 3D reconstructions of the vessel and stent. In our experience this possibility was used twice.

Results

We have performed 257 intravascular ultrasound scans at various stages of the procedure and one IVUS during coronary angiography at the stage of diagnostic examination. 93 intravascular scans were obtained at initial stage, and 49 – after predilatation. Initial IVUS during such procedures allowed to specify the importance of the stenosis and to determine the degree of the lesion in the main and the side branches, as well as provided the opportunity to define the character of stenosing masses distribution and to predict their eventual redistribution after stenting. The construction and the analysis of the third, longitudinal IVUS projection, allowing for a more clear and a less subjective evaluation of the above factors, was of paramount importance. Besides, baseline IVUS contributed to the adequate choice of the stent with the account of the difference between the proximal and the distal reference diameters, the true extension of the lesion, with the verification of eventual involvement of the "reference" segments; also, it allowed to select optimal balloons for subsequent post-dilatation, including with the use of kissing technique. At mid-term stage (when an additional manipulation was needed after IVUS), 17 scans were performed. During control IVUS after stent(s) implantation and post-dilatation manipulations, we evaluated the deployment of the stent, its position in relation to the bifurcation, the maintenance of the side branch patency. Besides, control IVUS determined the necessity of additional manipulations in the main and the side branches, as well as allowed to preplan control coronary angiography in case of necessity. Control IVUS revealed dissections in the main or the side branches in 7 cases, and in 4 of these cases additional stenting was necessary. In 4 cases the study revealed insufficient stent deployment with a significant residual plaque volume, which required additional manipulations with a larger balloon or a higher pressure. Marked elliptic stent deformation was revealed in 3 cases and also required additional dilatation. Finally, the malapposition of the proximal stent segment revealed in 5 patients also was corrected with balloon dilatation. During the final stage of the procedure we performed 98 intravascular ultrasound examinations, that confirmed optimal or satisfactory results of the intervention. Just as during the initial stage, the evaluation of the longitudinal reconstruction of IVUS data with a meticulous analysis of all the details during axial rotation was very important for the reliability of final ultrasound evaluation.

The implantation of dedicated bifurcation stents was technically successful in 100%. At the same time, in some cases the stent delivery was associated with technical problems.

Firstly, one has to note the necessity of a meticulous predilatation, as the profile of the delivery system used for dedicated bifurcation stents commonly is higher in comparison with the system for the ordinary stents. The main problem during the insertion of stents delivered with two guidewires (platforms Nile and Twin-Rail) consists in the possibility of their torsion. This require closer attention during the insertion of the guidewires and the advancement of the stents. When Nile platform is used, there are special technics allowing to re-advance one of the guidewires. The platforms of stents produced by Abbott (cobalt-chromium stent Multi-Link Frontier and Everolimus-eluting XienceSBA) are delivered with one monorail guidewire, then the second guidewire is shaft-advanced into the detached side-branch balloon, and the whole system is self-centered at the bifurcation carina. Despite apparent cumbersomeness, this delivery system in, in our opinion, one of the most handy and steerable. Fig. 4 presents the results of the first implantation of Xience SBA stent in the area of the bifurcation of the RCA in Russia.

It is necessary to mention another mandatory condition for a successful stent implantation – good support and residual diameter of the guiding catheter, preferably 7 F, and in this connection the femoral approach is the approach of choice for the implantation of the above systems. The positioning of BIOSSLim stents is technically far more easy, as there is no necessity to use the second guidewire, and different diameters of the proximal and the distal ends of the stent allow to optimize their adaptation to the vessel's lumen. In the same time, it is necessary to account for the weakening of stent construction just at the critically important site of bifurcation, and to be maximally attentive while performing kissing-post-dilatation after stenting. Finally, the implantation of Tryton stent is essentially a modification of the Culotte technique and requires, firstly, the use of an additional stent in the main branch (most often, a DES), and secondly, the most meticulous postdilatation.

After endovascular intervention all patients had good immediate results. There was one side branch thrombosis at day 2 after the pro-

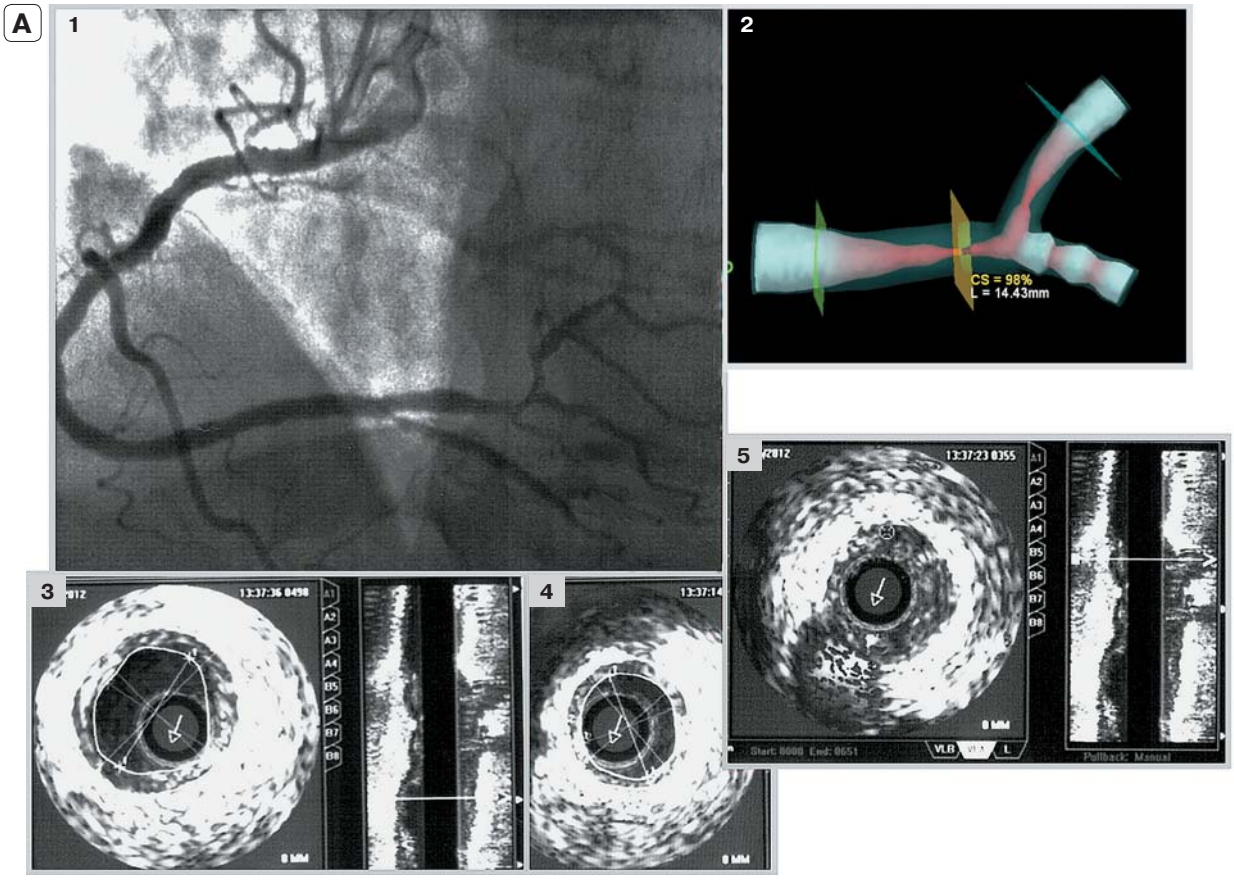
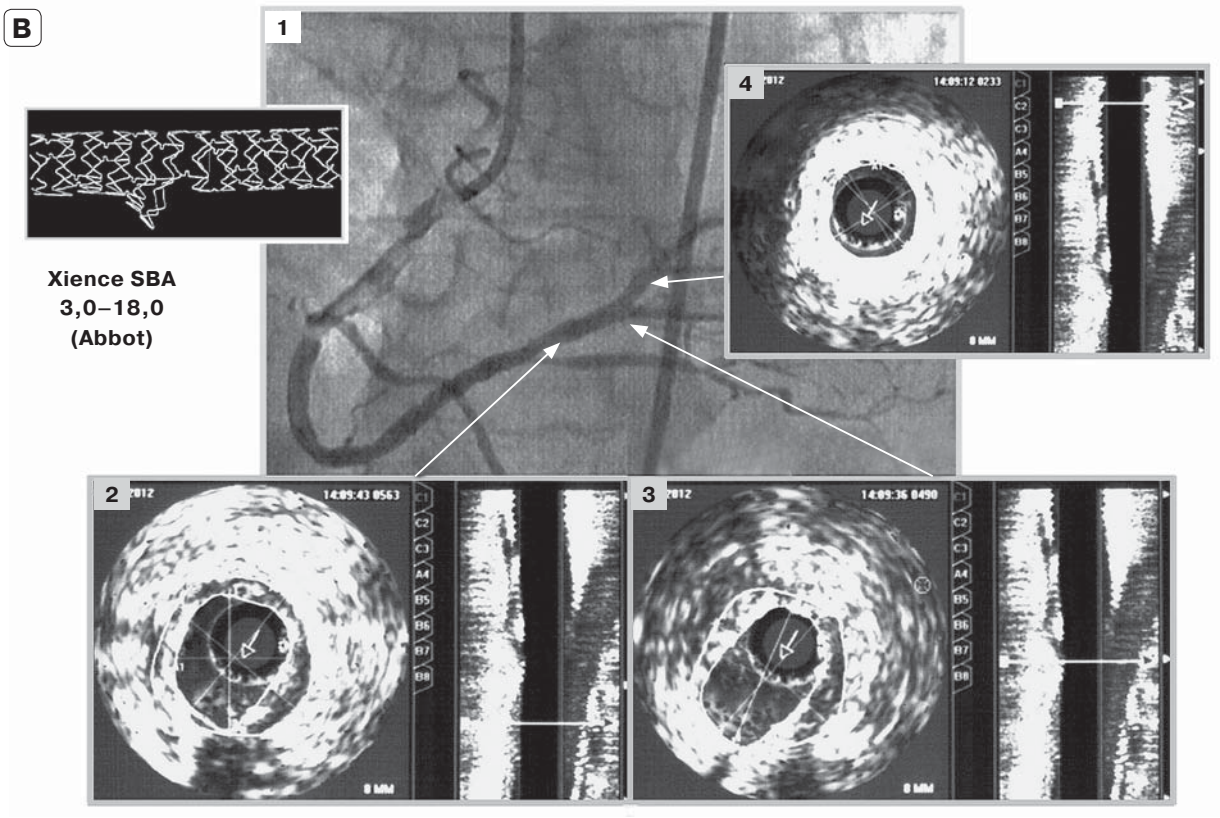


Figure 4. First implantation of Everolimus-eluting stent Xience SBA in Russia.
A – data of pre-stenting study: 1 – baseline angiography: critical stenosis in the area of RCA bifurcation; 2 – virtual 3D angiography; 3 – 5 – IVUS after predilatation with 2,0 × 20,0 mm balloon: 3 – proximal reference segment, 4 – distal reference segment, 5 – stenosis in the bifurcation area with a big plaque, marked positive remodeling of the vessel.



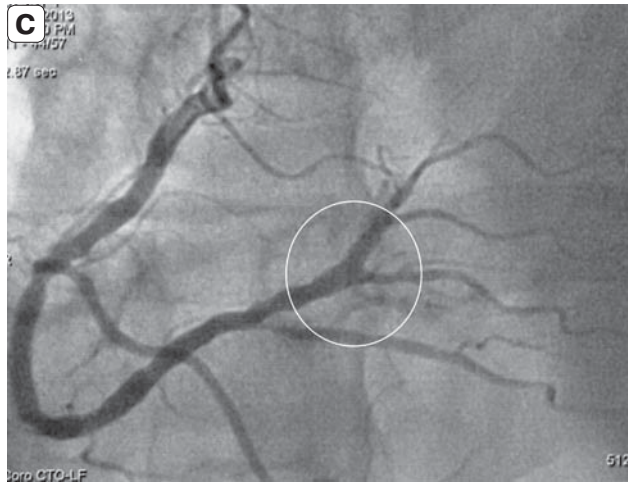


Figure 4.
B – data of control study after stenting with Xience SBA 3,0 × 18,0 mm: 1 – control angiography; 2 – proximal part of the stent after proximal adaptation; 3 – a part of stent at the bifurcation level, the elliptic form corresponds to the sile of two branches "confluence"; 4 – the segment of the artery distal to the stent. The third projection allows for good visualization of an optimal bifurcation form with completely patent main and side branches.
C – angiogram in 1,5 years after the procedure. Good patency of all branches is preserved in the area of reconstruction.

cedure (recanalization and stenting with DES were performed). Control coronary angiography was performed in 36 patients within 2 months to 8 years. The control was performed for clinical indications if patient's condition deteriorated or during staged interventions in other arteries. Another 64 patients underwent telephone survey. Thus, in total, long-term follow-up was obtained in 100 patients (63.3%).

Angiographic control of 38 dedicated bifurcation stents was performed in 36 patients. As a result, restenosis was revealed in 18 stents (including one urgently implanted stent). Restenosis in the main branch was found in 7 cases, in the die branch – in 4, in both branches – in 7 cases (in one patient the main branch restenosis was associated with side branch occlusion). In two patients the process progressed with the involvement of the proximal (in relation to bifurcation stent) segments of the artery. Restenosis was focal in 10 cases and diffuse in 8 cases. In 3 cases restenosis was revealed in the Paclitaxel-eluting stent (Nile Pax), in 1 case – in the Sirolimus-eluting stent (BIOSSLim), in the remaining 14 cases in-stent stenosis was revealed in bare metal stents.

In 8 cases restenosis were corrected by balloon angioplasty: of both branches using an ordinary balloon – 3, of one branch using an ordinary balloon – 1, of one branch using

a drug-eluting balloon – 1, of the main branch using a drug-eluting balloon and of the side branch using an ordinary balloon – 2, of both branches using drug-eluting balloons – 1. DES were implanted in 7 patients: in 5 cases – in the main branch (in two of these cases balloon angioplasty of the side branch was performed), and in 2 cases – in the side branch. Restenosis in the side branch was not corrected in 2 patients without clinical signs. One patient, who had restenosis in the bifurcation of the CxA, occluded stentin in the LAD and process progression in other segments, was referred for CABG.

The telephone survey performed in 64 patients revealed postoperative improvement in 57, stable condition without deterioration in 6 and a subjective deterioration in 1 patient. In the long-term 3 patients from the followed group suffered myocardial infarction. Hence, among 100 patients who underwent angiographic control or answered telephone survey within 8 years after the procedure, positive effect was preserved in 81%.

Discussion

In total, the rate of restenosis among the operated patients was 11.6%, with a rather significant difference between the groups of drug-eluting (4.7%) and bare metal stents (19.2%). The comparison inside the pairs Muli-Link Frontier(25%) – Xience SBA (0%) and Nile Croco(31.3%) – Nile Pax (5.9%) suggests that stent design is less important than the presence or the absence of drug-eluting coating. The rate of restenosis in the group with “true” bifurcations was 17.9%, in the remaining subgroups – 8.3%.

There was a rather dramatic difference in the rate of restenosis in groups with and without periprocedural IVUS use – 8.9% and 33.3%, respectively. One has to note that this difference can be partially explained by the fact, that the group without IVUS comprised also patients with complex lesions or technical problems during the procedure, which by itself could cause suboptimal results. However the effectiveness of routine use of intravascular imaging seems to be clearly demonstrated. For this reason we designate the operations with the use of dedicated bifurcation stents as “special cases of stenting” (25), when intravascular imaging should be used routinely. The reconstruction of the third, longitudinal projection of the ultrasound image is more important than in other cases. During control examination at the end of the procedure, additional information can be received from the construction of a 3D image on the base of OCT data, and the value of this image will probably increase.

Our experience with the use of dedicated bifurcation stents suggests, that this type of endografts should necessary be available in the cathlabs. Despite a rather high price in comparison with the linear stents, the use of dedicated bifurcation stents is cost-effective in patients who otherwise would receive two stents. The first criterion to be considered while solving the problem of the reasonability of using bifurcation stents, is the involvement of a large (>2.5 mm in diameter) side branch, including with its eventual extended lesion.

One of the problems with dedicated bifurcation stents consists in the limited size range, firstly in what concerns the length. Hence, the next criterion is the length of the lesion, which should be relatively short in order to be covered by a dedicated stent. Otherwise, the operator should have the possibility to prolongate the stented segment in proximal or distal direction.

A special case is represented by bifurcation lesion of 0,0,1 type, when the plaque is concentrated in the ostium of a large side branch. This branch can not be neglected in view of its clinical significance, while any other type of procedure inevitably leads to the compromise of the main artery. Various types of bifurcation stents allow to solve this problem in a variety of ways, including the stenting of the main artery (mandatory with DES), the stenting with the passage to the side branch, the use side branch stents in combination with an additional stent in the main branch.

Finally, the decision on the possibility of using bifurcation stents should be based on individual characteristics of endografts. Some stents (e.g., Twin-Rail) have clearly insufficient (1.5 mm) diameter of side branch balloon, which requires additional manipulations with device exchange. Most stents delivered with two guidewires present difficulties with the insertion in case of markedly angulated vessel; firstly, it concerns the circumflex artery. As already mentioned above, the diameter of the majority of bifurcation stents is bigger than those of the standard stents, for this reason femoral approach and guiding catheter of 7F at least are preferable options.

Conclusion

Thus, the use of bifurcation stents for the correction of lesions in the area of the origin of

large coronary side branches is an effective method allowing for adequate correction of this type of arterial lesions with good immediate and long-term clinical results. The obtained data show, that the site of lesion, the type of bifurcation stenosis, the degree of stenosis, the length of the lesion do not significantly limit the use of such stents. The use of dedicated bifurcation stents offer the opportunity to perform a more anatomy-friendly correction, provides more protection for the side branch during the whole procedure, minimizes the damage of the stent structure. The anatomical variability of the lesions requires the use of different dedicated bifurcation stents. In order to improve clinical results it is necessary to aim to the use of dedicated drug-eluting stents. Taking into account complex anatomy of bifurcation stenosis, routine use of intravascular imaging with mandatory construction of the third projection or 3D reconstruction is of great importance for the positive result of intervention.

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Clinical Issues of Optical Coherence Tomography for Coronary Diagnosis

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5-year experience of optical coherence tomography (OCT) used in elective and emergency coronary interventions was analyzed. 2638 procedures were performed at diagnostic and interventional stages. OCT is routinely used for balloon angioplasty involving drug-eluting balloons for in-stent restenosis and bioabsorbable scaffolds implantation, dynamic monitoring of the intervention results as well as for complex or angiographically uncertain cases including acute coronary syndrome. Our approaches to technical issues of the procedure with modification of certain generally accepted guidelines are presented.

Keywords: *optical coherence tomography, coronary stenting, intravascular visualization.*

Objective. To analyze the main clinical applications of optical coherence tomography in elective and emergency diagnostic and treatment coronary interventions.

Methods. 2638 coronary interventions using optical coherence tomography were performed over 5 years (from 2010 to 2015, inclusively) in the Department of Radiosurgical Techniques for Diagnostics and Treatment (RSTD&T) of Orenburg Regional Clinical Hospital. The procedures were performed using two OCT devices of two leading manufacturers. Both devices have 3D-reconstruction option: one device – in the on-line mode, another – in the post-processing mode.

Results. The majority of procedures was performed as a part of intraoperative assessment of the interventional results and dynamic monitoring (at Month 6 and Year 2) in the randomized trial named Orenburg. Moreover, OCT is routinely used for balloon angioplasty involving drug eluting balloons for in-stent restenosis and bioabsorbable scaffolds implantation. The accumulated clinical experience allows us to successfully use optical coherence tomography to solve difficult clinical problems, including emergency interventions for acute coronary syndrome. The article presents our approaches to technical issues of the procedure with modification of certain generally accepted guidelines.

Conclusions. OCT provides the highest resolution among available clinical options for invasive and non-invasive vascular imaging (10–20 μm) to perform high-precision measurements in vessel lumens and walls. Therefore, it offers benefits when visualizing intraluminal structures and vessel inner membrane/stent, identifying unstable plaques and blood clots, edge dissection, stent malapposition and underexpansion, measuring neointimal area. OCT can potentially be a “gold standard” not only in scientific research but also in routine clinical practice.

Introduction

A little over 10 years ago, in 2005, in clinical guidelines on intravascular ultrasound (IVUS) (1) comparing IVUS and other intravascular visualization options we noted that optical coherence tomography was the only method able to compete with or even supersede intravascular ultrasound. And we completed the analysis with the following wordings: “The future will show whether the optical coherence tomography will be used in clinical practice for cardiovascular diagnostics and how its availability, price and ease of use will compare with IVUS”. Rapid development of the method with quick change of several generations of devices and appearance of some manufacturers, development of 3D visualization methods and interface

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with angiographic imaging in just a few years gave a positive answer to the raised questions. Eventually, only 5 years later this method was introduced into practice and began to be used actively in our clinic.

The optical coherence tomography has several advantages allowing to replace intravascular ultrasound as the "gold standard" in scientific research: the highest resolution among the available clinical methods of invasive and non-invasive vascular imaging (10–20 μm), possibility of high-precision measurements in the lumen and vessel wall, superior accuracy compared to quantitative angiography and intravascular ultrasound, probe passage with maximum speed that accelerates the procedure, possibility to reconstruct clear and convenient for interpretation 3D images in different modifications.

Owing to the published expert and consensus documents, this method was standardized (2–4). The diagnostic value of OCT was repeatedly demonstrated in different clinical cases and various vessels (5). However, systematic approach to clinical applications of this method is still under development. A. Lotfi (6) considers that there are probable OCT-related benefits for assessment of optimal stent implantation (size, apposition, edge dissection), with better resolution compared to IVUS; possible benefits to evaluate the plaque morphology; at the same time the method should not be used to assess the significance of stenosis. Current clinical guidelines also cautiously evaluate clinical perspectives of optical coherence tomography. 2014 ESC/EACTS Guidelines on myocardial revascularization recognize OCT role in assessment of stent failure mechanisms and, in some patients, optimization of stent implantation (class IIB recommendation with level of evidence C) (7). Paradoxically, in the 2013 ESC Guidelines on the management of stable coronary artery disease, the role of OCT (along with IVUS) is somewhat broader, the methods can be considered to determine the lesion characteristics and improve the stent expansion (class IIB recommendation with level of evidence B) (8). The role of OCT is not defined in the 2011 US Guidelines on myocardial revascularization (9).

It's quite important that lesions detected by OCT and not verified with angiography and/or IVUS are fairly common, but their influence on clinical consequences requires further investigation and not proved yet. There are some articles concerning edge dissection (10, 11), biodegradable scaffolds implantation (12), malapposition (11, 13), relationship of the dissection, malapposition and stent healing (14).

However, indications for optical coherence tomography in which the method is rather clearly demonstrates its clinical benefits, are under development. These include bifurcation lesions (in which the possibilities of 3D-imaging are demonstrated most clearly), including implantation of special bifurcation stents (15–17), treatment of in-stent restenosis with cutting balloons and drug-eluting balloons (18, 19), interventions for acute coronary syndrome (20, 21).

It should be noted that in addition to recommendations from manufacturers, often too general, the published literature contain quite a little information on technical aspects of optical coherence tomography (22), which is of great importance for informative value and safety of the procedure. We think it is important to review these issues.

Materials and methods

In the Department of Endovascular Methods of Diagnosis and Treatment of Orenburg Regional Hospital the optical coherence tomography has been used for coronarography and reconstructive coronary interventions since December 2010. The first procedures were performed using C7-XR device, Light Lab Imaging Inc., which subsequently, when this company was taken over by St.Jude Medical, was modified up to Ilumien version. In addition to a new, more comfortable and ergonomic interface, the frame rate, maximum pullback speed, and maximum scan length were increased from 100 to 180 fps, from 20 to 36 mm/sec, and from 54 to 75 mm, respectively. The device uses the C7 Dragonfly catheter (maximum profile of 2.7 F), its mechanical high speed pullback is performed during the procedure.

The second OCT system used in the Department includes Lunawave device, Terumo, and FastView probe (maximum profile of 2.6 F). This system has possible frame rate varying from 30 to 160 fps, speed pullback from 0.5 to 40 mm/sec, and maximum scan length up to 150 mm. This complex also applies a mechanical high-speed probe pullback. This device was also modified; its latest version is able to reconstruct 3D intravascular images quickly in the operating room.

In turn, St.Jude Medical has implemented this feature in its new generation devices – Ilumien Optis. Despite the fact that this version

of the device was not available in Russia at the time of writing this article, we can perform 3D reconstruction of Ilumien OCT images using the off-line mode on a dedicated workstation (Ilumien Optis offline review workstation). Finally, our St. Jude Medical device has one more function, i.e. the ability to measure fractional flow reserve using special wire probes and Wi-Box unit that receives information from the probe via Wi-Fi.

This article analyses 2638 OCT procedures performed in our Department from December 2010 to October 2015. By the end of March 2016, the total number of procedures exceeded 2800. This extensive experience helped us to develop our own approaches to the technical aspects of the procedure with modification of some guidelines. Moreover, not all technical parameters of the procedure are described in detail in the literature. We believe that the following items can be extremely helpful for OCT beginners.

1. Access and size of the guiding catheter. The femoral access and guiding catheter ⩾7F without side holes are the conventional guidelines. These requirements though acceptable for interventions lead to significant limitations during the diagnostic stage and follow-ups. Empirically, 6 F guiding catheter with side holes provides high-quality images; therefore, transradial access can be used more extensively. Adequate choice of the type and curve of the guiding catheter is fundamental to ensure its coaxiality with the target vessel. In our experience, the use of OCT does not affect the choice of access for intervention and procedure.

2. The route of administration of contrast media. Of course, automatic syringe with manual control (ACIST CVi or analogues) is preferable. The speed and injection volume of contrast media are accurately adjusted (ultimately, savings are achieved), and the artery is filled homogenously and tightly providing the highest quality and informative value of the procedure.

3. The injection parameters of contrast media. In real practice, the required amount of contrast media to obtain high-quality image is somewhat larger than usually reported in the literature. The optimal injection rate and volume of the contrast media are 4 mL/sec and 15 mL in the left main coronary artery and/or proximal parts of the left anterior descending artery and circumflex artery. In the middle and distal parts of the circumflex artery and left anterior descending artery, the rate is increased up to 5–6 mL/sec, and volume is enlarged up to 16–18 mL, sometimes (with caution) up to 20 mL. In the proximal part of the right coronary artery the recommended rate of contrast injection is 4 mL/sec and the volume is 14 mL; in the middle and distal parts – 5 mL/sec and 16 mL, respectively, in rare cases the volume can be increased with caution up to 18 mL.

4. Pullback speed and pullback start mode (manual or automatic). Although the maximum pullback speeds allow examination of greater portions of the vessel per contrast injection, images of the highest quality and complete information can be obtained easier at average pullback speeds (20 mm/sec for Ilumien and 25–30 mm/sec for Lunawave). We prefer the manual pullback start since in this case the operator can see a tight bolus, perform pullback start and achieve fully adequate filling of the vessel while the automatic pullback start, especially in cases of prolonged lesions, can occur when the vessel is not adequately filled, resulting in a large number of artifacts in the distal part of the target area.

5. Distal introduction of the catheter. Of note, the tip of the catheter is approximately 1.5–2.5 mm distal to the contrast mark and shifts distally by additional ~5–10 mm when the contrast media is injected; therefore, this method is contraindicated for very distal lesions due to absence of free space for the probe and high risk for arterial perforation. The probe should always be on the guidewire! In addition, small diameter of the vessel prevents lumen filling with a fluid required for light wave passage and distal location requires higher rate and larger volume of contrast media.

6. Introduction of the catheter in difficult anatomical settings. The probe catheters have the mini-rail structure and are quite fragile. Therefore, the catheter should be introduced very carefully (slowly and non-forcefully) in highly tortuous and/or calcified vessels, otherwise, the likelihood of the probe damages is quite high. In such cases, two standard guidewires or standard and “hard” (support) guidewires can be preventively applied. As pushability of the probe is limited, its progress can be greatly hampered by some anatomical features of the coronary arteries, e.g., orifice of the circumflex artery at the right or acute angle. In the latter case, the Lunawave catheter may be preferable.

7. Long lesions. Several pullbacks (most often two) are required in long native or stented lesions. In this case, marker portion should be

included in both pullbacks to match the images. After stenting, it is a place of stent overlap, in native vessels it is one of the major side branches. In the case of stenting, the pullback should be started at least 0.5 cm distal to stented segment and end at the ostium of the vessel. It is necessary to assess stent apposition and exclude the edge dissection.

8. Procedure for pronounced left-dominant coronary blood flow. In case of pronounced left-dominant coronary blood flow with the left main coronary artery, LAD, and CA of large diameters, the procedure may be inappropriate as quality images cannot be obtained because the vessels cannot be filled tightly despite large volumes of injected contrast media.

9. Procedure for critical impairment. Of note, the liquid medium conducting the light is mandatory to obtain images. Therefore, you should not attempt to use OCT for critical lesions or occlusions without pre-dilation (even if a friable thrombotic substrate is assumed).

10. 3D image reconstruction. To built a high-quality 3D reconstruction of OCT images, the target section of the vessel should be limited, average probe speed (10–20 mm/sec) is to be set and optimal volume and rate of contrast injection should be selected.

Results

Given the significant advantage of optical coherence tomography concerning the resolution and image quality, it is primarily used for visualization of the inner surface of the vessel (or stent) and intraluminal structures, especially when the stenting results are controlled.

The greatest number of these procedures in our Department is associated with the randomized trial Orenburg (comparison of the drug-eluting stent implantations guided by IVUS or angiography) (23). The study design involved optical coherence tomography at the final stage of intervention to record its results, and then together with the control angiography at Months 6 and 24.

1032 patients were included in the study during primary enrollment which lasted 36 months. OCT was performed in 1020 patients, 676 out of them previously had intravascular ultrasound. At Month 6, 930 patients were followed up, 890 out of them had OCT. At Year 2 (at the time of preparing this article) 667 patients were followed up (OCT was performed in 659 patients).

According to the study protocol, intraoperative OCT was performed after optimal stenting results confirmed by IVUS were achieved. However, the results of optical coherence tomography performed as a post-stenting follow-up demonstrate an unexpectedly large number of findings indicating suboptimal implantation compared to IVUS and especially angiography results. The good stenting results with optimal stent expansion (achievement of its nominal size, eccentricity index > 0.75), no stent malapposition or tissue prolapse were observed in 471 patients (45.6%).

The suboptimal results based on OCT data and optimal results according to IVUS data were observed in 171 patients (25.3% in the IVUS group); the suboptimal results in the angiography group, when solely OCT was performed at the final stage were obtained in 187 patients (52.5%). Finally, the suboptimal results based on both IVUS and OCT data were observed in 195 cases (28.8% in the IVUS group). Thus, while there was no optimal stent expansion according to the IVUS data in a quarter of cases, OCT documented suboptimal results in more than a half of the patients from both groups.

Plaque prolapse after stenting was observed in 371 cases (35.9%). To characterize this phenomenon, we used two parameters calculated based on the most representative frames: tissue protrusion area and tissue protrusion area/luminal area ratio. The tissue protrusion area varied from 0.1 mm^2 to 11.77 mm^2, with the average tissue protrusion area of 0.83 ± 1.12 mm^2. The tissue protrusion area/luminal area ratio varied from 0.1% to 29.24% (mean – 7.6 ± 5.04%).

OCT revealed malapposition of stent struts in 146 patients (14.3%) (defined as incomplete stent strut apposition to the intima at the distance of at least one stent strut thickness). Malapposition varied from 0.15 to 1.1 mm. It should be noted that in 79 patients from this group (54%) the stent sizes were chosen based on the IVUS data and OCT was preceded by a follow-up IVUS. Moreover, all patients underwent postdilation with larger balloon and/or higher pressure. In these settings, the reported malapposition rate is quite high. In addition to malapposition, 52 patients had tissue protrusion. 29 patients out of them had IVUS at baseline and follow-up.

12 patients out of 1032 had no OCT or the obtained results were not informative. This could be for two reasons: anatomical features and arterial diameter. In two cases, OCT was not informative due to pronounced left-domi-

nant coronary blood flow, large diameter of the LMCA, LAD, and CA; as a result, adequate tight filling of the vessels to obtain high-quality images suitable for interpretation was not achieved. In eight cases, it was impossible to conduct OCT probe (of different manufacturers) due to anatomical features of the coronary artery orifice (circumflex artery in 4 cases) or pronounced arterial kinking and calcinosis. One of the objectives of the Orenburg study is to assess the impact of post-stenting problems revealed by OCT only and not determined by IVUS.

In addition to evaluating the stenting results, optical coherence tomography is of great importance for more accurate identification of intraluminal problems during interventions or diagnostic procedures when making a decision on further treatment.

In 10 patients angiography revealed the contrasting defects which were differentiated between incomplete stent expansion and plaque prolapse through the stent struts. In three of these cases, OCT confirmed stent patency without struts deformation, although the oval shape of the stent was revealed in the middle part which was related to its underexpansion in one of the planes due to severe calcinosis (Fig. 1).

In two patients, OCT revealed a diastasis between the implanted stents; however, clinical consequences were different. In one of these cases, OCT verified no intimal dissection, insignificant stenosis, and sufficient residual area in the interstent gap and, accordingly, no additional intervention was needed. On the contrary, in other case, a marked plaque with lipid component and dissection was observed in the diastasis area and delayed angiography revealed increase in the filling defect requiring additional stenting (Fig. 2). Moreover, optical coherence tomography determined subintimal location of the guidewire in the posterior descending artery (stenting was preceded by recanalization of chronic occlusion of the right coronary artery). Under OCT and IVUS guidance, the guidewire was re-conducted in the true arterial lumen not affecting the distal blood flow.

Another subgroup consisted of 10 patients in whom OCT confirmed or revealed a significant prolapse of friable plaque elements and white thrombi. Angiographically uneven opacification was suspected in a half of these cases. 8 out of 10 patients were randomized in the Orenburg study. At final follow-up, OCT identified a marked prolapse and/or large masses of blood clots requiring administration of glycoprotein IIb–IIIa inhibitors and additional stenting in three cases (Fig. 3). These three patients were excluded from the study. At Month 6, angiographic follow-up was performed in all eight patients; follow-up optical coherence tomography was done in 6 patients (including all five remained in the study). OCT confirmed satisfactory results, i.e. smooth contours of the neointima without its pronounced growth. Out of two patients who underwent angiographic follow-up only, one had good angiographic and clinical outcome, another had RCA-related instent occlusion.

Two notable cases concerned the right coronary artery. The target lesion in both cases was located in the middle part of the RCA. However, coronary angiography identified a layering of contrast medium resembling the second contour of the proximal part. In the former of these cases, IVUS did not clarify the situation. OCT revealed the enlargement and double lumen of the artery with longitudinal trabecular structure of about 12 mm. The stenting covering the proximal part of the RCA was performed. Follow-up OCT determined the incomplete compression of the second lumen and stent malapposition in its proximal part. When additional angioplasty was performed using a balloon of larger diameter, follow-up OCT showed full stent apposition and no false lumen (Fig. 4). In the second case, the situation was largely identical, however, IVUS was not performed, and an intervention was guided by OCT.

Since introduction of optical coherence tomography into the practice of our Department in 2010 and at least for two years, the main indication for its routine use was interventions using drug-eluting balloons for in-stent restenosis. The drug-eluting balloons are one of the promising treatment options for in-stent restenosis in the coronary arteries. As for reliable results of repeated interventions it is important to achieve maximal reduction of the neointimal volume with its minimal injury, we have been using intravascular ultrasound from the first angioplasties with drug-eluting balloons (since 2008) (24). The appearance of optical coherence tomography has provided the possibility to obtain images with a resolution 10 times higher compared to IVUS. While the experience with OCT for DEB-associated angioplasty was accumulated, the approach to these interventions has been changed. If OCT was previously used to record the results after using the drug-eluting balloon, it is now proven that OCT

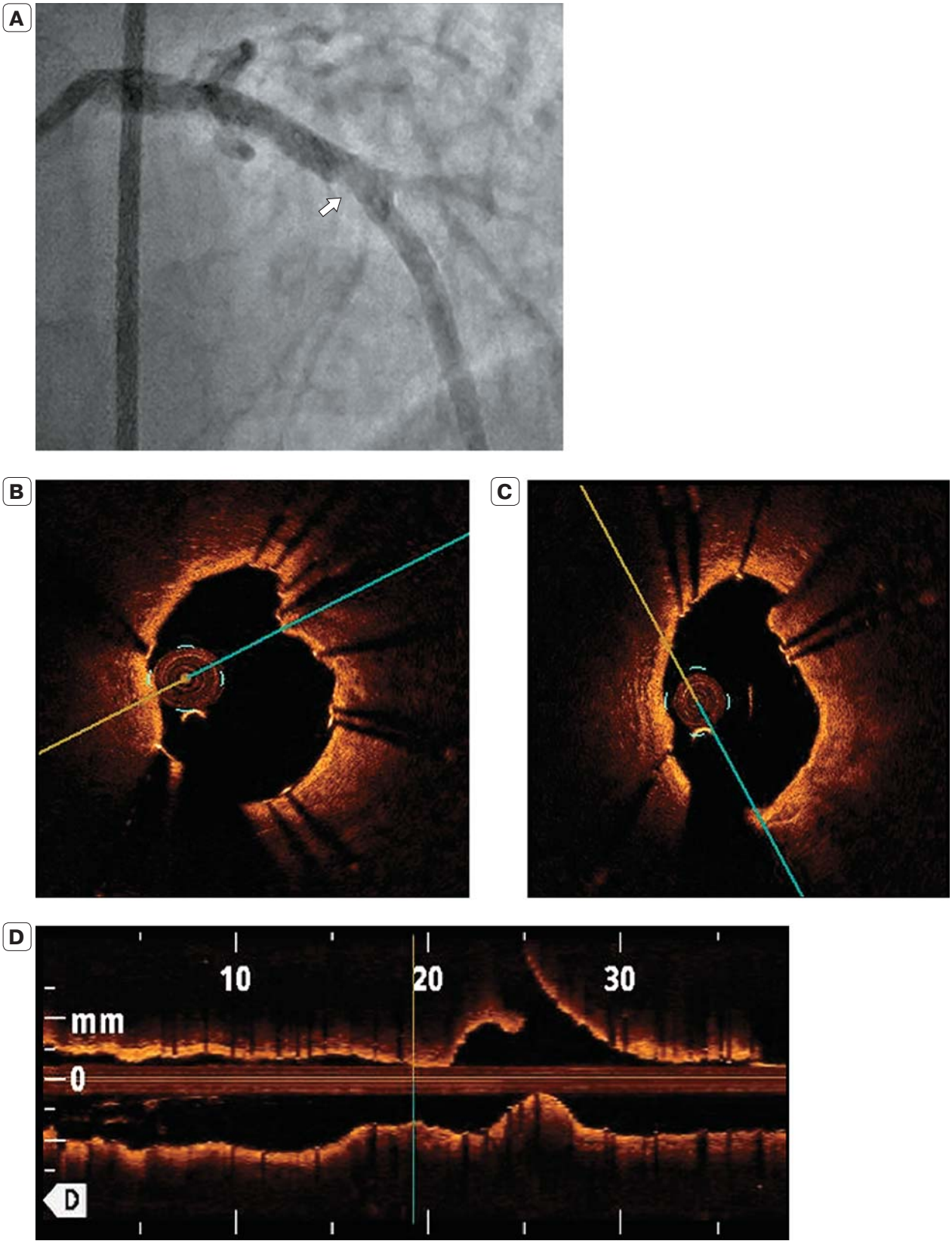

Figure 1. Stent deformation caused by severe calcinosis.
A – the angiogram shows an in-stent lucency at the level of the diagonal branch (arrow).
B, C – there is a clearly visible oval and slightly irregular shape of the stent due to severe calcinosis at 12–14 hours although any damaged stent structure is observed neither on transverse nor on longitudinal (D) images.

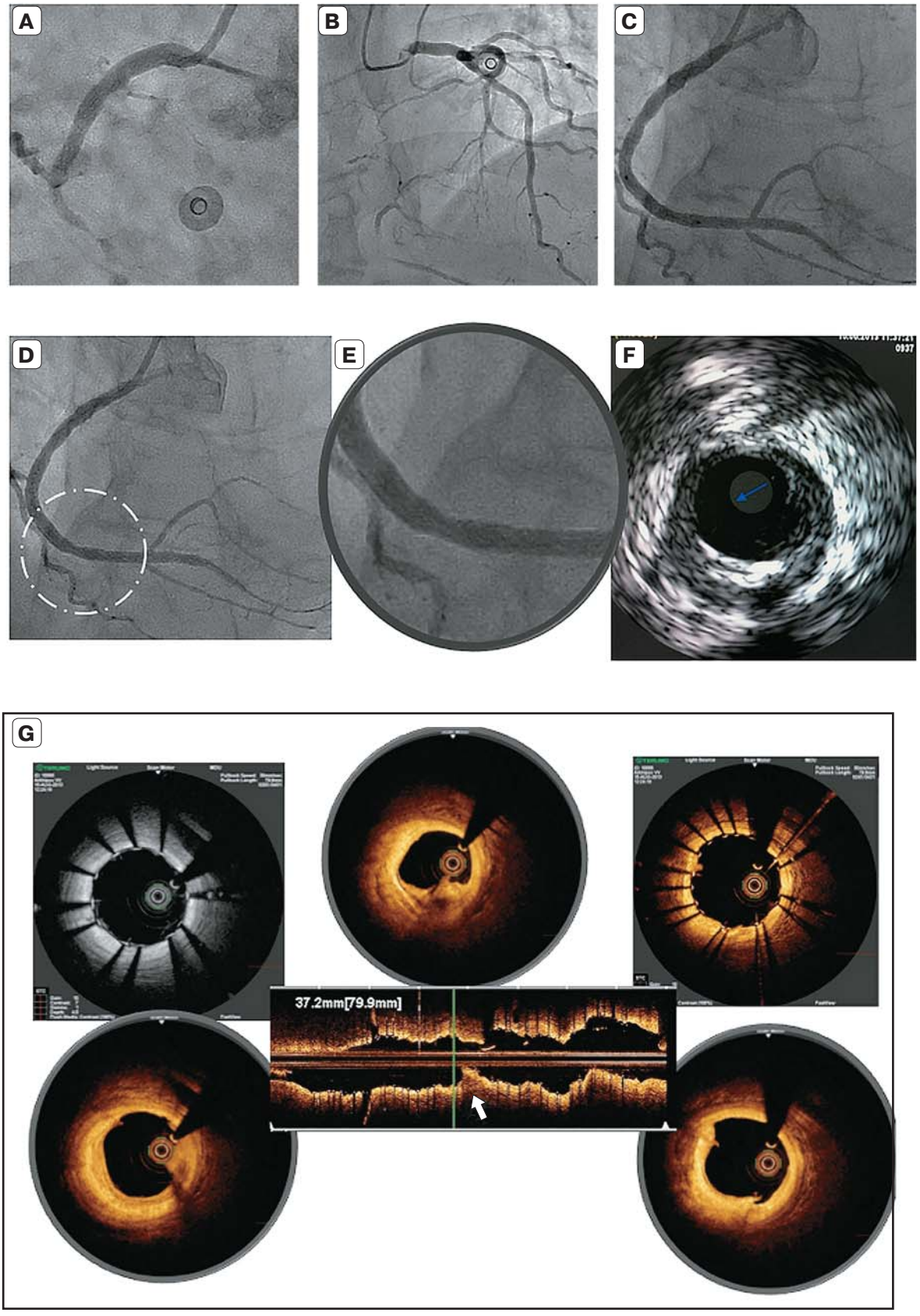

Figure 2. Dissection between the stents.
A, B – original occlusion of the right coronary artery.
C – angiographic result after the implantation of two stents.
D, E – delayed angiography suspected diastasis between the stents.
F – diastasis confirmed by IVUS.
G – OCT confirmed the diastasis and revealed progressive intimal dissection (arrow).

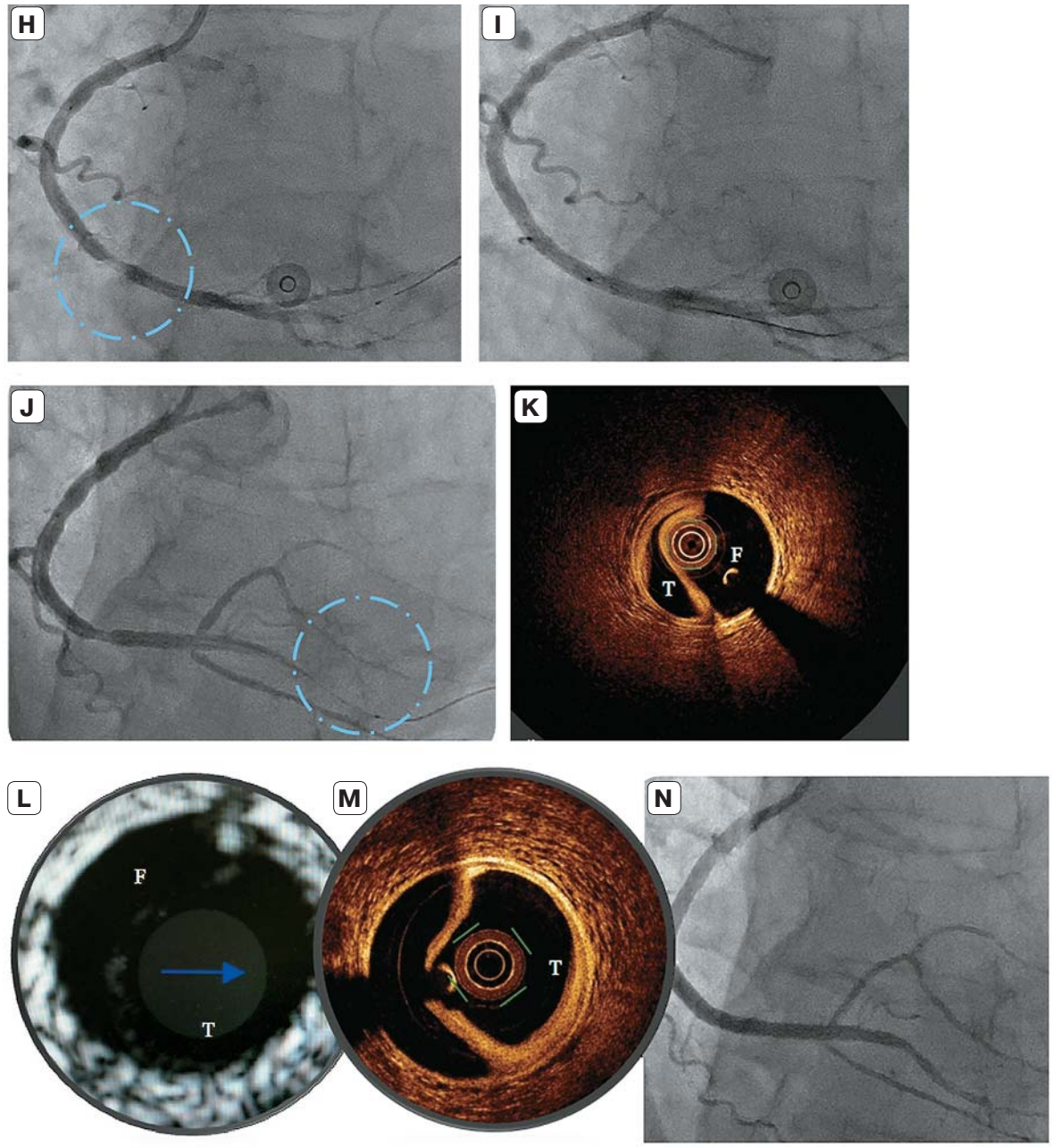

Figure 2.
H – repeated angiography identified the increase in filling defect; decision was made to implant an additional stent.
I – results of additional stenting.
J – no filling of the peripheral branch, incorrect position of the wire was suspected.
K – OCT verified position of the wire in false lumen (F) with collapsed true lumen (T).
L – the wire was readvanced in the true lumen under IVUS guidance.
M – OCT confirmed the correct position of the wire. Additional manipulation was not performed because of the expansion of the true lumen and the compression of the false lumen.
N – good angiographic results.

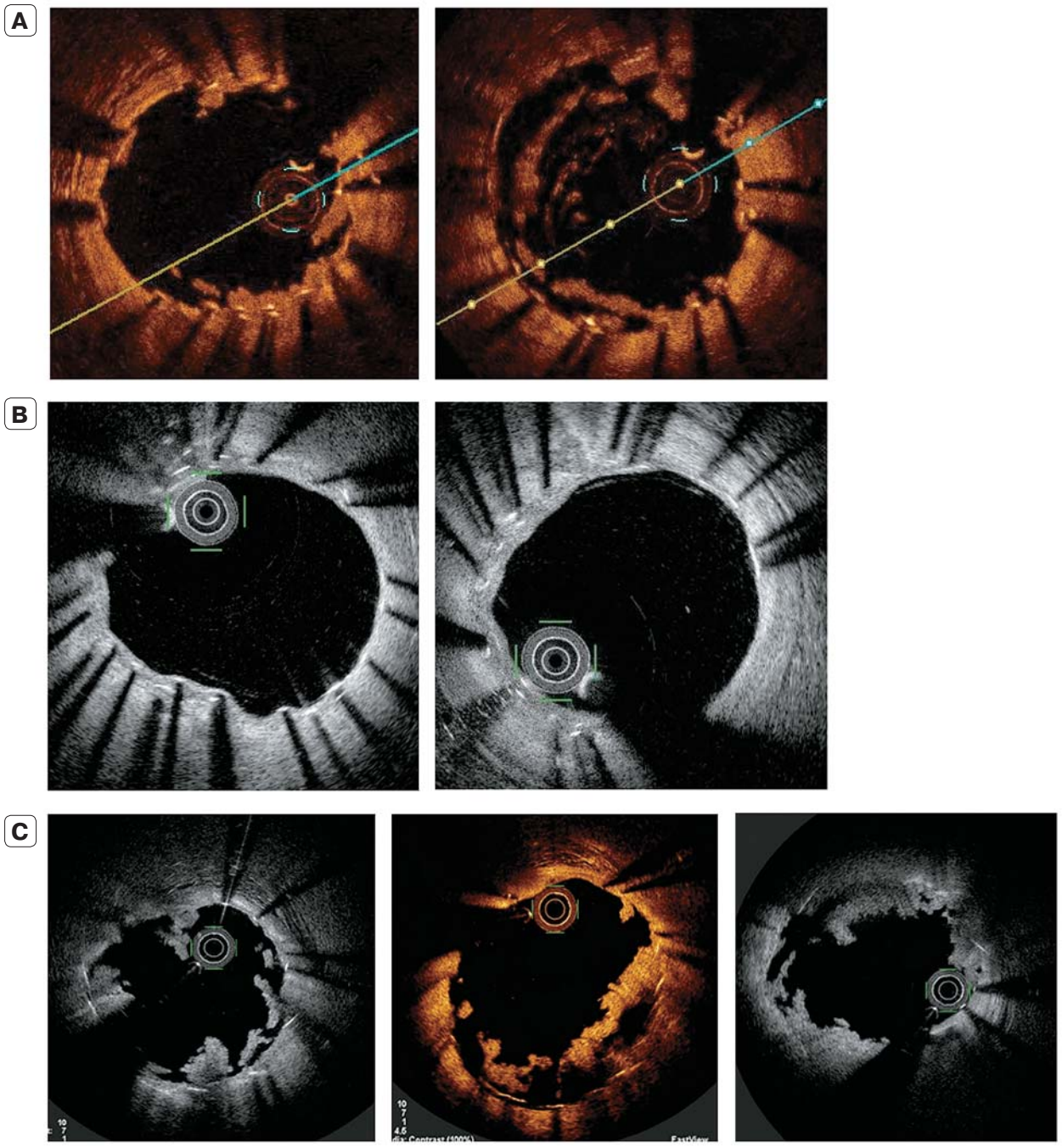

Figure 3. The prolapse of friable plaque components with elements of thrombosis.
A – moderate – volume prolapse with inclusion of the white blood clots. The intervention was complemented by the administration of glycoprotein IIb-IIIa inhibitors.
B – follow-up at 6 months. Complete healing, good endothelialisation, no intimal hyperplasia.
C – severe prolapse of atheromatous masses with superposition of thrombi. Additional stenting was performed.

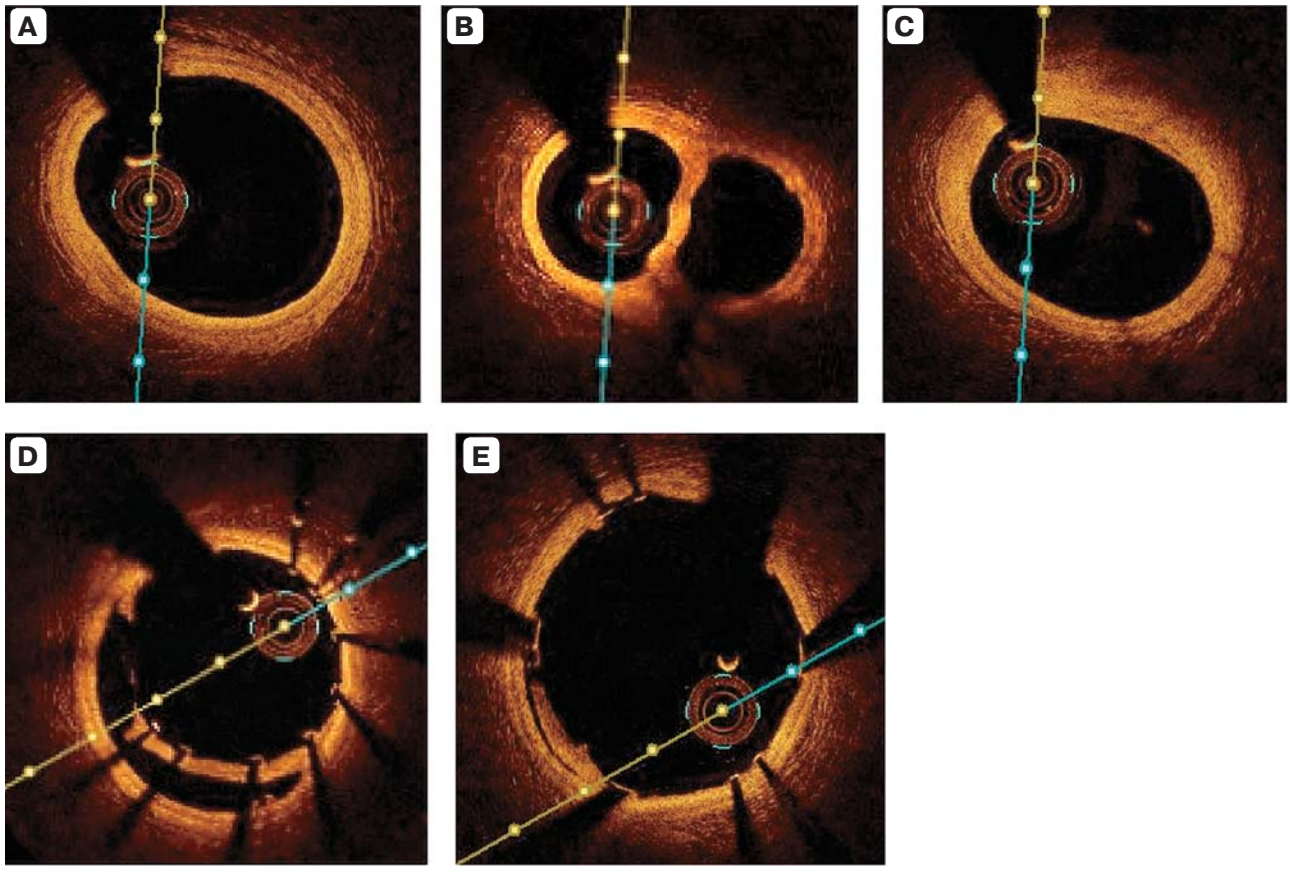

Figure 4. Double lumen of the right coronary artery.
A – proximal reference segment.
B – double lumen segment, the area of the main lumen is 3.05 mm^2.
C – distal reference segment.
D – intermediate results after stenting – incomplete compression of the second lumen, malapposition, the area of the lumen is 6.58 mm^2.
E – results after additional angioplasty – good apposition, the area of the lumen is 9.6 mm^2.

is more informative and important for clinical outcome when used prior to the drug-eluting balloon after achievement of satisfactory angiographic results following predilation with conventional balloon,. OCT confirms the efficacy of predilation and lack of severe intimal dissection which is a prerequisite for the drug-eluting balloon.

195 interventions using optical coherence tomography were performed in 135 patients. The procedure was performed during intervention in 119 patients (interim or final control). The dissections sometimes with thrombus masses were observed in 10 cases (only a half of them were angiographically severe); therefore, we decided to refuse from drug-eluting balloons in favour of drug-eluting stents.

Follow-up coronary angiography with OCT at Month 6 after DEB application was performed in 86 patients, 70 out of them had OCT during the intervention, in remaining cases, IVUS was used.

Owing to the high resolution of optical coherence tomography, the neointimal area was measured precisely and directly. At Month 6, the neointimal area increased on average by 13.6% only suggesting sufficient efficacy of the drug-eluting balloons for in-stent restenosis. The reduction in thickness and neointimal area was observed in 33.3% and 30% patients, respectively, confirming the drug impact on cell growth. The follow-up examination was uninformative in two patients due to distal lesion and small diameter of the target vessel (an effect of catheter “beating” that creates additional artifacts appears).

OCT not only quantifies the neointimal growth but also qualitatively characterizes post-angioplasty healing. In two cases, angiographic follow-up revealed borderline stenosis of ~55%, however, when the OCT data was assessed, the stenosis area was ~70%. These patients were implanted with drug-eluting stents.

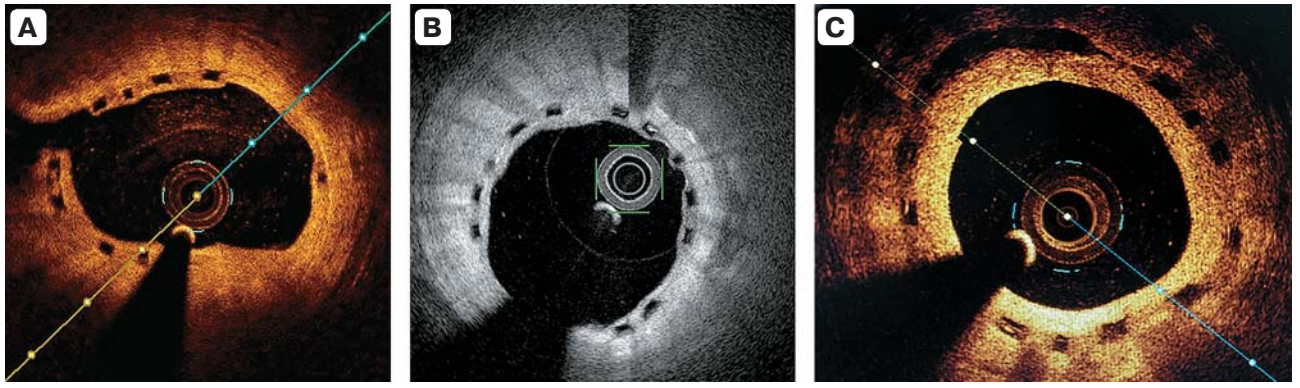

Figure 5. The scaffold degradation at different time points after implantation (the data obtained from different patients).
A – Month 13. Unchanged struts at 10–11 hours, endotelialized struts at 12, 3, 7 hours, initial destruction at 9 hours.
B – Month 24. The majority of struts are endotelialized, the strut is not changed at 2 hours, and destruction started at 1 hour.
C – Month 36. Scaffold struts are at different stages of destruction including slightly changed struts at 1–2 hours and those almost completely resorbed without full tissue replacement at 10–12 hours.

Currently, in our hospital OCT is obligatory for interventions with drug-eluting balloons and follow-up of long-term results (at Month 6 after intervention).

Another "obligatory" indication for OCT in our experience is biodegradable scaffolds. The motivation for this includes two main reasons. Firstly, even the first experience with these devices has shown a great role of strict compliance with rules for their implantation as well as accurate sizing due to their technological features. In this regard, intravascular imaging, of course, is superior over angiography and IVUS has some advantages compared to OCT. Secondly, as demonstrated by the initial clinical experience, the resorption of scaffold is heterogeneous, uneven, and controversial; with accumulation of the long-term results it became clear that the resorption was not limited to two years mentioned originally. The new time point for complete degradation of the implant is 5 years. Thus, by the time the scaffolds appeared in our market, it became clear that a responsible approach to the patients requires the implantation of these devices to be accompanied by a careful follow-up for their resorption.

The absorbable scaffolds were firstly implanted in our Department in January 2013, and OCT has been applied since these first interventions. Totally, 47 procedures were performed in 23 patients from January 2013 to January 2016. In 5 patients OCT was performed at baseline (determination of reference sizes of the artery, length of the lesion, selection of the balloon of adequate size to prepare the vessel for scaffold implantation) or after predilation with the same purpose. The intravascular ultrasound which provides more detailed information on the sizes of the vessel and plaque was used in the remaining patients to achieve the same objectives. OCT was performed in 23 patients at the final stage of the intervention to control apposition of the scaffold, adequacy of expansion and lack of mass prolapse into the stent lumen. At Month 6, angiography and OCT were performed in the first six patients. The analysis showed that these procedures are uninformative because stent degradation is not manifested macroscopically at this time point. Subsequently, it was decided to perform follow-up procedures at 1-year intervals. To date, nine patients were followed up at Month 12/13, three patients were followed up at Month 24, and two patients were followed up at Month 36. Follow-up procedure determines the neointimal thickness, state of the implant (degree of strut resorption) as well as degree of neointimal coverage of the struts. Our results are consistent with the published data suggesting heterogeneous degradation of the scaffold when both unchanged and more/less degraded struts and connectors are observed on the same cross section (Fig. 5). At Month 24 follow-up, the struts not covered with neointima were observed in two patients; therefore, they were recommended to continue clopidogrel.

When optical coherence tomography is used for dynamic control of scaffold resorption, a new feature of the latest generations of OCT devices – 3D image reconstruction is particularly informative. High-quality 3D-image clearly shows the destruction areas as well as the de-

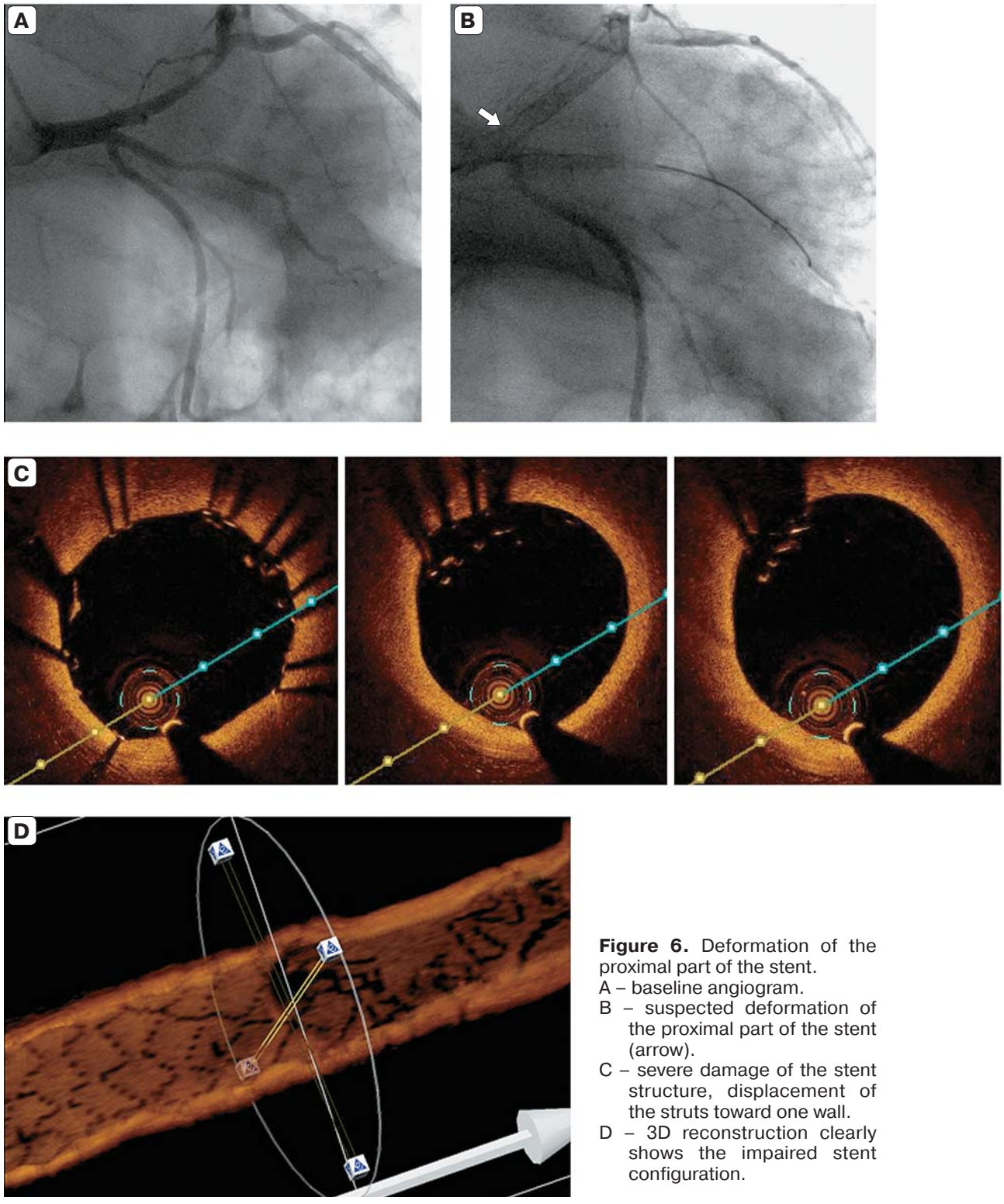

Figure 6. Deformation of the proximal part of the stent.
A – baseline angiogram.
B – suspected deformation of the proximal part of the stent (arrow).
C – severe damage of the stent structure, displacement of the struts toward one wall.
D – 3D reconstruction clearly shows the impaired stent configuration.

gree of stent endothelialisation. As information obtained from one cross-section is rather limited and analyzed sections are randomly selected, the ability to visually assess the spatial structure of the stent using 3D reconstruction is very valuable. Moreover, the generated 3D image greatly facilitates comprehensive analysis of the vessel and stent via free rotation in any plane.

The intravascular imaging in emergency coronary pathology, for obvious reasons, is much rarer than in elective interventions. However, OCT has also been used in these cases after procedure improvement and accumulation of our own experience. Eight emergent procedures were performed in five patients. In four patients OCT was used to confirm the stenosis significance and verify the causes of filling de-

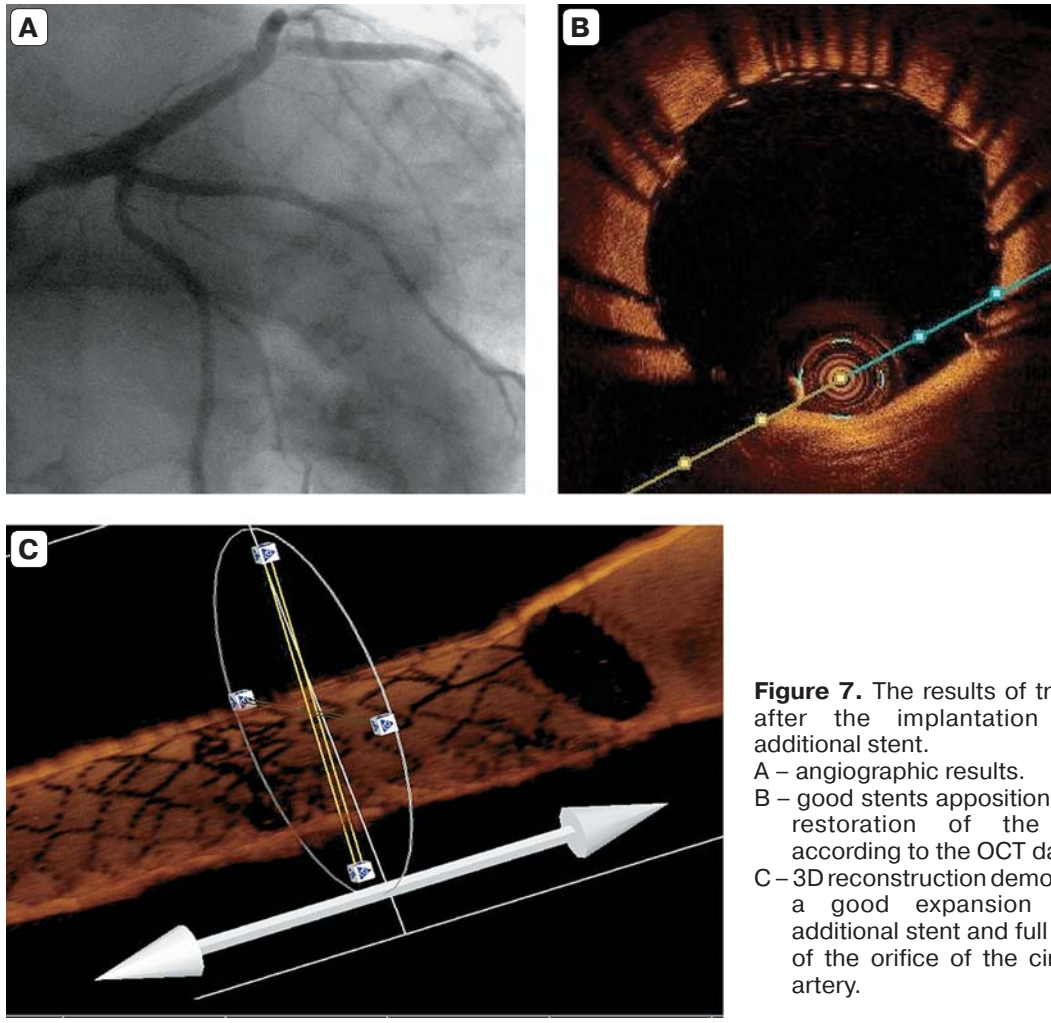

Figure 7. The results of treatment after the implantation of an additional stent.
A – angiographic results.
B – good stents apposition with full restoration of the lumen according to the OCT data.
C – 3D reconstruction demonstrates a good expansion of the additional stent and full patency of the orifice of the circumflex artery.

fects (lucency, turbulence areas) in the native artery, stent or adjacent arterial segments. In two patients after thrombolysis (and borderline stenosis according to the angiography data) OCT revealed significant thrombotic masses requiring stenting. In one case of angiographically uncertain lesion (differentiation between calcinosis and mural thrombotic masses was required), OCT confirmed the presence of both structures and the intervention was completed with stenting. On the contrary, in another patient OCT verified calcinosis proximal to the implanted stent with hemodynamically irrelevant stenosis degree; therefore, the intervention was completed.

The following case is of special interest (Fig. 6). Angiography revealed the stenosed left anterior descending artery and intermediate artery, the LAD was stented from its orifice and postdilated; the large diagonal artery was opened via the stent strut with good angiographic results. However, after stent placement in the intermediate artery and serial control angiography, deformation of proximal stent struts at the LAD orifice was suspected. OCT confirmed deformation of of circumference of the stent proximal segment. The stent structure with its normal apposition was preserved only along one arterial wall. Another stent overlapping the destroyed part of the previously implanted stent was implanted; the stents were additionally adapted and follow-up OCT was performed. Stent placement from the orifice was confirmed with the good lumen and full apposition of the stents along their entire circumference. The retrospectively reconstructed 3D image even more clearly demonstrates both a stent-related problem and the final results (Fig. 7).

Conclusion

OCT provides the highest resolution among existing clinical methods of invasive and non-invasive vascular imaging (10–20 μm) to perform high-precision measurements in the lumen and vessel wall, differentiate the tissue structure like histological differentiation.

Although OCT is inferior to IVUS concerning the penetrating ability and not always visualizes

the entire vascular wall thickness, luminal measurements in reference segments gives the opportunity to adequately choose the parameters of stent implantation and postdilation option, and OCT has definite advantages in relation to visualization of intraluminal structures and the intima/inner layer of the stent. Optical coherence tomography also has a greater potential than IVUS for visualization of unstable plaques and blood clots.

In cases when quantitative angiography may not clearly describe the affected segment (intraluminal thrombotic masses, lucency, filling defects), OCT adequately evaluates the lumen enabling to choose the optimal treatment strategy. The method used for immediate follow-up after stenting provides an opportunity to identify such problems as edge dissection, stent malapposition, red and white blood clots, stent underexpansion. Timely detection of the above listed problems helps to make adequate corrections and obtain optimal immediate and long-term results. This feature becomes especially important in anatomically difficult segments and complex lesions (bifurcation, left main coronary artery, overlapped stents, decision on completing intervention without stenting).

High resolution OCT for the first time provided an opportunity for precise direct measurement of the neointimal area. This is especially important in the era of the drug-eluting stents and can affect the duration of desaggregant therapy via objective assessment of the feasibility of its continuation or termination.

Owing to continuous technological improvement, reliability of quantitative results, high resolution and image quality the value of optical coherence tomography will increase and it will become the "gold standard" not only in scientific research but also in routine clinical practice.

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The Drug-Eluting Balloons for Coronary Arterial Restenosis: 7-Year Experience

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The article presents 7-year experience with various drug-eluting balloons for intracoronary in-stent restenosis. The drug-eluting balloons were used in 212 patients. At follow-up, the incidence of re-stenoses after drug-eluting balloons was 21.7%. Great attention is paid to compliance with technology of the balloon impact; own modified technique is proposed; the importance of intravascular visualization is shown; the long-term results of these interventions are presented.

Keywords: *coronary angioplasty, coronary stenting, drug-eluting balloons, in-stent restenosis, intravascular ultrasound, optical coherence tomography.*

Objective. To analyze the experience with drug-eluting balloons for intracoronary in-stent restenosis; to demonstrate the ability of intravascular imaging to optimize intervention and assess its results over time.

Methods. For correction of in-stent restenoses 212 interventions using the drug-eluting balloons were performed, most interventions – with intravascular imaging guidance. Four types of paclitaxel-eluting balloons were used, i.e. SeQuent Please, Dior, In.Pact Falcon and Protégé. From 2008 to 2010, IVUS, and then OCT were used to control postoperative results and follow-ups in 3-6 months. Since 2011, OCT has been mostly used after in-stent predilation just before DEB inflation and at Month 6 Follow-up. The second significant modification of the standard technique is application of drug-eluting balloon with diameter 0.25–0.5 mm greater than diameter of the implanted stent at the main stage of the intervention.

Results. Intraoperative IVUS and OCT were performed in 69 and 119 patients, respectively. Follow-up invasive procedures were performed in 167 patients (85.2% of the total number of patents who were required to be followed up at the specified time points) including 39 and 110 patients who had IVUS and OCT, respectively. The incidence of restenoses in 3–6 months after DEB impact was 21.7%.

Conclusions. Angioplasty using drug-eluting balloons expands the treatment options for intracoronary stent restenosis. DEB requires no fundamental change in interventional technique and does not make the intervention difficult. The compliance with technique of drug-eluting balloons and adequate preparation of the vessel are of great importance for achievement of favourable immediate and long-term outcomes. IVUS and OCT used for intraoperative qualitative and quantitative control of DEB-related interventions increase the efficacy of these interventions, prevent intraoperative complications, and reliably evaluate the long-term results.

Introduction

Although the immediate and long-term results of endovascular treatment for occlusive and stenotic coronary lesions are favourable, particularly after drug-eluting stents were widely introduced in real practice, the increasing numbers of interventions and patients with multivessel or diffuse coronary disease are inevitably associated with the increasing total number of patients requiring re-interventions for restenoses in the stented vessels.

The various techniques were used to manage the intracoronary in-stent restenosis at different times and the repeated conventional coronary balloon angioplasty is the most common (and still used) option. Although this technique is widely used, the incidence of restenoses after these interventions is quite high (1, 2). The cutting balloon angioplasty is more

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effective but much less common technique. Despite advantages in management of restenoses, the cutting balloons are quite rarely used for this purpose due to technical features of the device (poor deliverability), on the one hand, and its high price on the other.

Bare metal stents used for restenosis have no advantages over primary stenting in terms of restenosis while the length of stented segment and metallization area are increased (2).

The drug-eluting stents are the most effective treatment option for restenoses. However, their application is associated with all problems related to the drug-eluting stents including the necessity of prolonged dual antiplatelet therapy, high cost of the device, and remaining problem of additional metallization of the vessel. The disadvantage of drug-eluting stents used for both native stenosis and in-stent restenosis is uneven distribution of the drug coating along the vascular surface dependent from struts architecture which leads to heterogeneous inhibition of cell proliferation and subsequently to uneven stent endothelialisation.

A new treatment option for coronary restenosis (so-called drug-eluting balloon – DEB or drug-coated balloon – DCB) has been developed in the last decade. The potential advantages of the drug-eluting balloons include: reduction of re-stenosis incidence compared to conventional angioplasty with no increase of interventional complexity; opportunity to avoid an additional metallization of the vessel; immediate drug release without using a polymer which can cause inflammatory response; decreased necessity of antiplatelet therapy; potentially more homogeneous delivery of the drug to the vascular wall and consequently more even endothelialisation compared to the drug-eluting stents (3).

The effective impact of the drug-eluting balloons is based on potential inhibition of proliferation of vascular smooth muscle cells for prolonged period after short-term contact with the lipophilic antiproliferative substance. The drug is delivered when the balloon is inflated; the delivery matrix dissolves and paclitaxel penetrates into smooth muscle cells (4). A sustained antiproliferative effect on the smooth muscle cells with no cytotoxic effect is observed after single application. The sufficient paclitaxel tissue concentration is achieved when the balloon is inflated for 30 sec. The peak concentration is observed in 45 sec, and if the inflation time is 60 sec, the paclitaxel can be traced in the blood but disappears in the next 10 minutes (5).

The first drug-coating balloon which became commercially available and was validated in clinical trials was SeQuent Please, B/Braun, using Paccocath DEB technology. During manufacturing the conventional balloon catheter is covered with paclitaxel at a dose of 3 μg/mm^2 in conjunction with non-polymeric matrix which is a contrast medium – iopromide. Due to hydrophilic nature of iopromide and lipophilic properties of paclitaxel the drug homogenously releases and penetrates into the vascular wall. The efficacy of this device for coronary in-stent restenosis was shown in PACCOCATH ISR I/II trials (Efficacy and Safety of Paclitaxel-Coated Balloons in Coronary In-Stent Restenosis). These trials involved 108 patients with coronary in-stent restenosis who were randomized into two groups: conventional balloon angioplasty and drug-eluting balloon angioplasty. The 6-month, 12-month and 2-year trials showed superiority of the drug-eluting balloons over conventional balloons, namely less repeated revascularizations and lower incidence of major cardiovascular events (6, 7).

Another pivotal trial was PEPCAD II ISR (The Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease to Treat In-Stent Restenosis: A Comparison to the Paclitaxel-Eluting Taxus Stent). The study involving 131 patients compared the safety and efficacy of the drug-eluting balloon SeQuent Please compared with Taxus stent for in-stent restenosis. The study has demonstrated the better outcomes for the drug-eluting balloon compared to the stent in relation to the binary restenosis incidence and late lumen loss rate. The 3-year follow-up revealed no significant differences between the groups concerning the repeated revascularization rate and major cardiovascular events rate, while their proportions were almost halved in the DEB group (8, 9).

The PEPCAD-DES trial (Treatment of Drug-eluting Stent [DES] In-Stent Restenosis With SeQuent Please Paclitaxel Eluting Percutaneous Transluminal Coronary Angioplasty [PTCA] Catheter) involved 110 patients with coronary restenosis in the drug-eluting stents who were randomized into two groups: Group 1 – the restenosis was treated with drug-eluting balloon SeQuent Please, and Group 2 – the restenosis was treated with a conventional coronary balloon. 6-month follow-up demonstrated that late lumen loss rate and repeated revascularization rate were significantly lower in the drug-eluting balloon group. At Month 36, the significantly lower rates of repeated revascula-

rization and major events were observed in this group – 19.4% vs 36.8% and 20.8% vs 52.6%, respectively (10).

The results obtained from PEPCAD China ISR trial (A Prospective, Multicenter, Randomized Trial of Paclitaxel-Coated versus Paclitaxel-Eluting Stent for the Treatment of Drug-Eluting Stent In-Stent Restenosis) are similar. This study compared the outcomes of restenosis treatment in the drug-eluting stents using the drug-eluting balloon SeQuent Please or drug-eluting stent Taxus Liberte in China. The study included 220 patients from 17 Chinese hospitals assigned equally into these groups; the primary endpoint was 9-month late lumen loss rate. At Month 9, coronary angiography revealed no difference in the late lumen loss rates between the groups. No significant differences were noted in both groups in relation to 1-year repeated revascularization rate (15.5% and 17.5 % in the DEB and DES groups, respectively), and major events rate (2.7% vs 6.8%) (11).

The method of drug delivery used in the DIOR balloon, Eurocor, originally was different from the SeQuent balloon, however, since 2009 the company switched to its new modification which used the concept similar to Paccocath. The efficacy of the DIOR balloon for in-stent restenoses is shown in the Valentines Trial (patient recruitment from February 14–23, 2010) which included more than 250 patients from more than 30 countries including the Russian sites (including 7 patients from the Orenburg Regional Clinical Hospital). 244 patients were followed up 6–9 months after intervention. The cumulative major cardiovascular events rate was 11.1%, and the repeated revascularization rate was 7.4%; thus, it was concluded that the DIOR 2nd generation balloon was effective and safe for in-stent restenosis (5, 12).

The In Pact Falcon balloon manufactured by Invatec has proprietary FreePac urea-paclitaxel coating. When the balloon is inflated, the coating comes into contact with the arterial wall while urea molecules separate and free the paclitaxel molecules increasing their solubility and facilitating their absorption into the arterial wall. The BELLO (Balloon Elution and Late Loss Optimization) trial conducted in 15 Italian sites and involving 182 patients evaluated the comparative efficacy of the In.Pact Falcon drug-eluting balloon versus Taxus drug-eluting stent in the small coronary arteries. The primary endpoint of the study was the 6-month late lumen loss which amounted to 0.09 ± 0.38 mm and 0.3 ± 0.44 mm in the In.Pact Falcon group and Taxus group, respectively. Moreover, the major events rate and repeat revascularization rate were lower in the drug-eluting balloon group – 10% vs 16.3% and 7.8% vs 11%, respectively. Thus, the study showed that the In.Pact Falcon balloon is a serious competitor to the Taxus stent in the primary interventions in the small coronary arteries (13). The largest range of sizes among all drug-eluting balloons is a major advantage of this balloon.

Pantera Lux, Biotronik, is one more balloon currently available on the market. This balloon, like others, uses a drug substance paclitaxel at the standard dose of 3 μg/mm^2 which is placed over the delivery matrix – butyryl-tri-hexyl citrate (BTHC). The efficacy of this balloon for in-stent restenosis after implantation of both bare-metal stents and drug-eluting stents was investigated in the prospective multicenter trial FIM. The 6-month follow-up data obtained from the first 45 patients were very successful: the major events rate was 7.7% which included only one post-procedural non-fatal myocardial infarction and two repeated revascularizations (one - for target vessel, one – for target lesion); late lumen loss amounted to 0.03 ± 0.35 mm. Therefore, a conclusion was made on the possible successful use of this drug-eluting balloon for in-stent restenosis after implantation of both the drug-eluting and bare metal stents (14).

The Danubio balloon, Minvasis, also has paclitaxel coating at a dose of 2.5 μg/mm^2 located in the butyryl-tri-hexyl citrate (BTHC) delivery matrix. The DEBSIDE study demonstrated potential of this balloon in combination with the Nile PAX stent for bifurcation lesions: the balloon used for angioplasty of the side branch after the bifurcation stent reduces lumen loss and restenosis rate in the side branch (15).

Finally, there is one more commercially available drug-eluting balloon – Protege, Blue Medical. Its special feature is the original location of the drug substance encapsulated in hydrophilic coating on the wings of the folded balloon (Wing Seal technology).

According to the above listing, almost all the drug-eluting balloons used in real practice have similar principal structures and use paclitaxel as a drug substance. Attempts have long been made to use sirolimus, which has some advantages over paclitaxel in the drug-eluting stents, for balloon coating. Nevertheless, a report about the commercially available sirolimus-eluting balloon appeared only recently (Magic

Touch, Concept Med.) In this case, a principally different concept of coverage with a drug substance is used, i.e. phospholipid encapsulated sirolimus nanocarriers, but it requires to be confirmed in clinical trials involving large populations (16). The dose is 1.27 μg/mm². However, the manufacturer reported impressive results of the first trials of this balloon, i.e. the target lesion revascularization and overall major cardiovascular event rate was 1.66% only among 120 intervented lesions at Month 12.

This article presents 7-year experience with various drug-eluting balloons routinely used for intracoronary in-stent restenosis.

Materials and methods

The drug-eluting balloons were used in 212 patients for intracoronary in-stent restenosis in the Department of Endovascular Methods of Diagnosis and Treatment of the Orenburg Regional Clinical Hospital from 2008 to 2015. The characteristics of patients and intervened arteries are shown in Table 1.

Four types of paclitaxel-eluting balloons were used, i.e. SeQuent Please (B/Braun), Dior (Eurocor), In.Pact Falcon (Invatec) and Protégé (Blue Medical). The distribution of balloons is shown in Table 2.

The drug-eluting balloons for restenosis were used after both the bare-metal stents (stainless steel and cobalt-chromium) and various drug-eluting stents were implanted (Table 3).

Two or three stents per coronary artery were primarily implanted in 73 patients (34.4%). In 4 cases, after the stents were implanted for in-stent restenosis the recurrent in-stent restenoses were treated with the drug-eluting balloons.

The drug-eluting balloons were used again in three patients. In one of these cases, the SeQuent Please balloon was initially used; in another case, the Dior balloon was initially used. The SeQuent Please balloon was used again in both cases. Three Dior balloons were initially used in the third patient with a relatively prolonged lesion, and this patient was re-intervened using In.Pact Falcon and Protege balloons. Two and three balloons per vessel were used simultaneously in 14 and 2 patients, respectively.

Initially, we adhered to standard technique for drug-eluting balloons which subsequently was slightly modified. The standard recommendations for drug-eluting balloons which are not principally different in various manufacturers are as follows: the drug-eluting balloon should have diameter equal to that of the implanted stent; the inflation time is from 30 seconds to 1 minute; the balloon should be inflated over one segment only, the additional balloons are required to cover the entire length of the lesion (according to early recommendations, the balloon could be moved and re-inflated, some manufacturers preserved this possibility to date); stenosed segment should be overlapped by at least 2 mm.

It is crucial to select appropriate lesions for this technique. In-stent angioplasty is more logical for focal restenosis, however, we consider it acceptable for sufficiently prolonged lesions. In the latter case, at least two criteria should be preferably followed: stenosis should not extend beyond the stent and the plaque should be preferably homogeneous and uniform.

Table 1. Characteristics of patients and intervened arteries

Parameter	Number	%
Gender		
Male	187	88.2
Female	25	11.8
Arterial hypertension	198	93.4
Diabetes mellitus:		
Insulin-dependent	2	0.9
Insulin-independent	17	8.0
Dyslipidemia	171	80.7
Left anterior descending artery	67	31.6
Circumflex artery	56	26.4
Right coronary artery	72	34.0
Obtuse marginal branch	13	6.1
Posterior descending artery	1	0.5
Posterolateral branch	1	0.5
Intermediate artery	1	0.5
Diagonal branch	1	0.5

Table 2. Used drug-eluting balloons

Balloon	Number of interventions
SeQuent Please	46
Dior	48
In.Pact Falcon	119
Protégé	7
Total	212 interventions (different balloons were used per one patient in 8 cases)

Table 3. Type of stents for primary stenting

Type of stent	Number of patients
Stainless steel stent	98
Cobalt-chromium stent	72
Paclitaxel-eluting stent	15
Everolimus-eluting stent	5
Sirolimus-eluting stent	8
Zotarolimus-eluting stent	2
Biolimus-eluting stent	12

The proper preparation of the stenosis to the treatment with the drug-eluting balloon is another important methodological issue. The initial angioplasty using conventional balloon before DEB impact is necessary in most cases. However, angiographic assessment of the initial angioplasty does not comprehensively review its efficacy. In many cases, angiography does not provide information on the residual stenosis, severity of intimal dissection, possible edge concerns within the stent. In case of unrecognized non-optimal predilation, the drug-eluting balloon does not lead to satisfactory outcome due to the factors unrelated to the drug-eluting balloon.

As we have a substantial experience with intravascular imaging, we have begun to use it for monitoring the intervention results since the first cases when the drug-eluting balloons were used. Since the first interventions with DEB we have used intravascular ultrasound to record the intervention results and obtain the data for further comparison in the long-term period (17). IVUS was performed using Oracle InVision (EndoSonics/Jomed/Abbott), s5 and s5i (Volcano) devices and Eagle Eye and Eagle Eye Gold phase-electron probe. As longitudinal measurements were not required, the manual probe pullback was preferably used. The measured parameters were as follows: the severity of intimal dissection (no more than 30% of the circumference, no severe flotation), residual neointimal thickness and stenosis degree relative to the stent lumen after impact, as well as appropriateness of the stent expansion and its conformity with the nominal values. Moreover, the patients underwent the programmed follow-up – angiography and IVUS to evaluate the stenosis degree, neointimal thickness and area, index of lumen loss. Initially, the follow-up was scheduled in 3–4 months. With accumulation of experience, it became clear that a possible restenosis after DEB angioplasty develops somewhat later compared with conventional balloons, therefore since 2010, the follow-up has been scheduled in 6 months.

Since 2010, optical coherence tomography once introduced in practice of our Department started to be used for follow-up to measure the same parameters as IVUS. Finally, since 2011 OCT has been preferably used during DEB angioplasty because of fundamentally new opportunities to evaluate the outcomes. In addition to significantly more accurate information on neointima status after predilation, optical coherence tomography is much more sensitive than IVUS for identification of intraluminal blood clots. OCT was performed using C7-XR/ Ilumien device (LightLab/ St. Jude Medical) and C7 Dragonfly probe and Lunawave device (Terumo) and FastView probe. Mechanical high-speed (20 to 40 mm/sec) probe pullback was used. The first ten patients had both IVUS and OCT to monitor the DEB angioplasty results. However, a few cases later when the inflation of drug-eluting balloon was followed by stenting (Fig. 1, 2), it was concluded that OCT was more informative and clinically significant if performed prior to inflation of drug-eluting balloon when angiographycally acceptable results were achieved after conventional balloon angioplasty. In this case, OCT confirms the adequacy of the performed impact and avoid using the drug-eluting balloon on the improperly prepared basis (Fig. 3). The significant residual neointima or severe intimal dissection can hamper effectiveness of the drug-eluting balloon (Fig. 4). OCT was used at this stage of the intervention in all subsequent patients (18).

The drug-eluting balloons 2.5 to 4.0 mm in diameter (on average, 3.3 ± 0.04 mm), and 15.0, 20.0, 25.0, 30.0, and 40.0 mm in length (on average, 26.5 ± 6.9 mm, in case of two or three balloons their lengths were summed) were used for final angioplasty. The average pressure for angioplasty using the drug-eluting balloon was 12.1 ± 2.4 atm and the exposure time was from 30 to 60 sec.

Results

The interventions using the drug-eluting balloons were performed within the period from 2 to 126 months after primary intervention (on average, 16.97 ± 20.09 months). Pre-interventional in-stent restenosis averaged 81.42 ± 10.93% based on angiography data; the post-interventional in-stent stenosis was 29.12 ± 11.95%, 36.51 ± 6.94%, and 46.96 ± ± 8.27% based on angiography, IVUS, and OCT data, respectively.

The follow-up invasive procedures were performed in 167 patients (85.2% of the total number of patents who were required to be followed up at the specified time points; the follow-up time point was not achieved by the time of analysis in 16 patients). 3-month and 6-month follow-up was performed in 46 and 113 patients, respectively; follow-up was performed beyond Month 6 in 8 patients (mostly up to 1 year after balloon angioplasty). According to the follow-up data, all patients

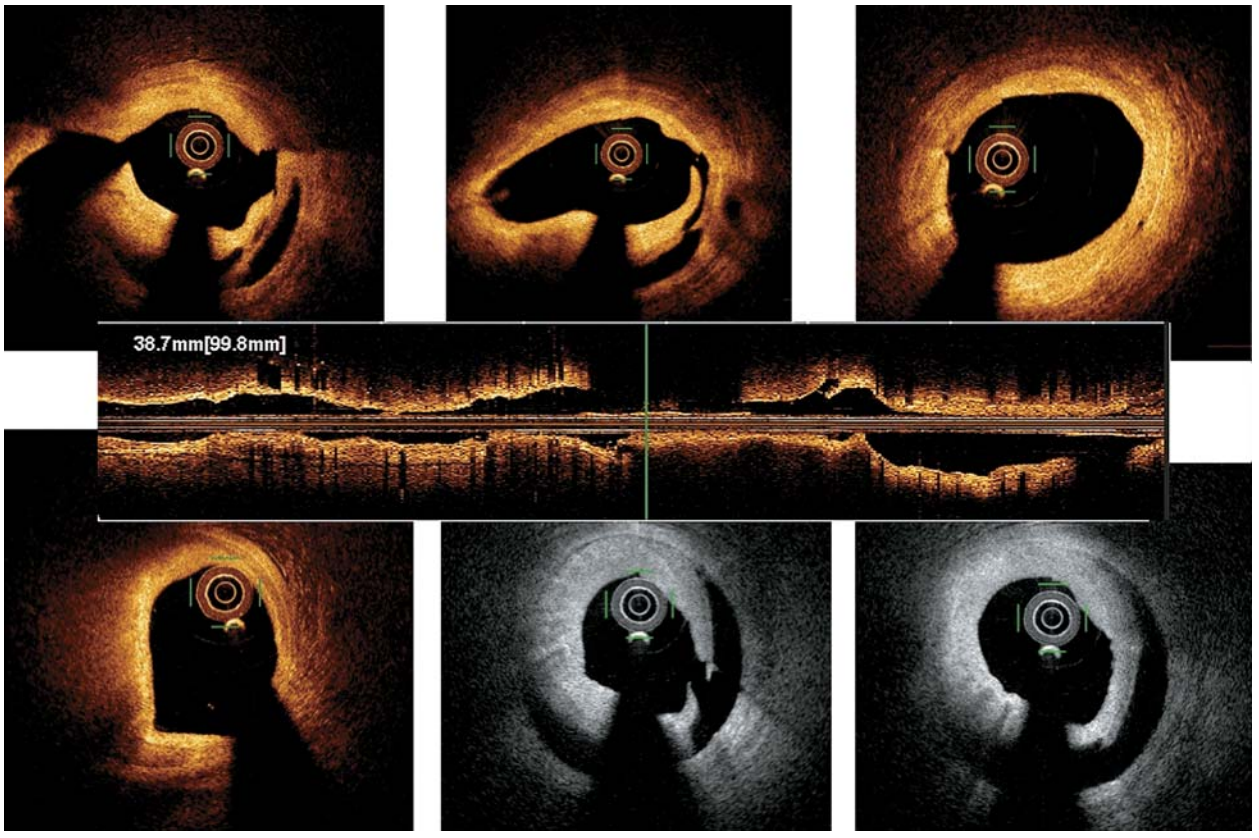

Figure 1. Follow-up OCT after dilation with DEB. Severe arterial dissection distal to the stent not visible with angiography was revealed. Additional stent was implanted. The arrows indicate the site of intervention.

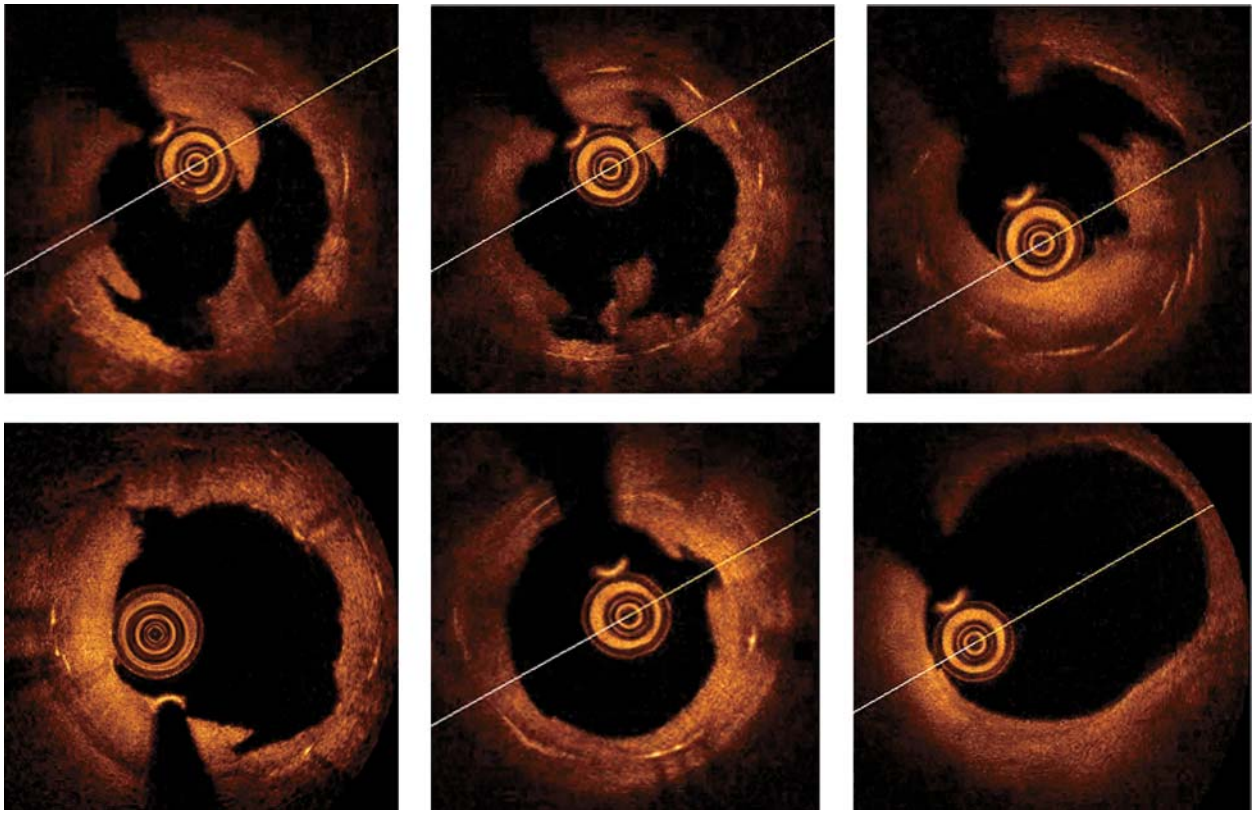

Figure 2. Follow-up OCT after angioplasty with DEB. In the angioplasty area, significant residual volume of the plaque and severe intimal dissection with flotation and thrombotic masses are identified in different segments. Drug-eluting stent was implanted.

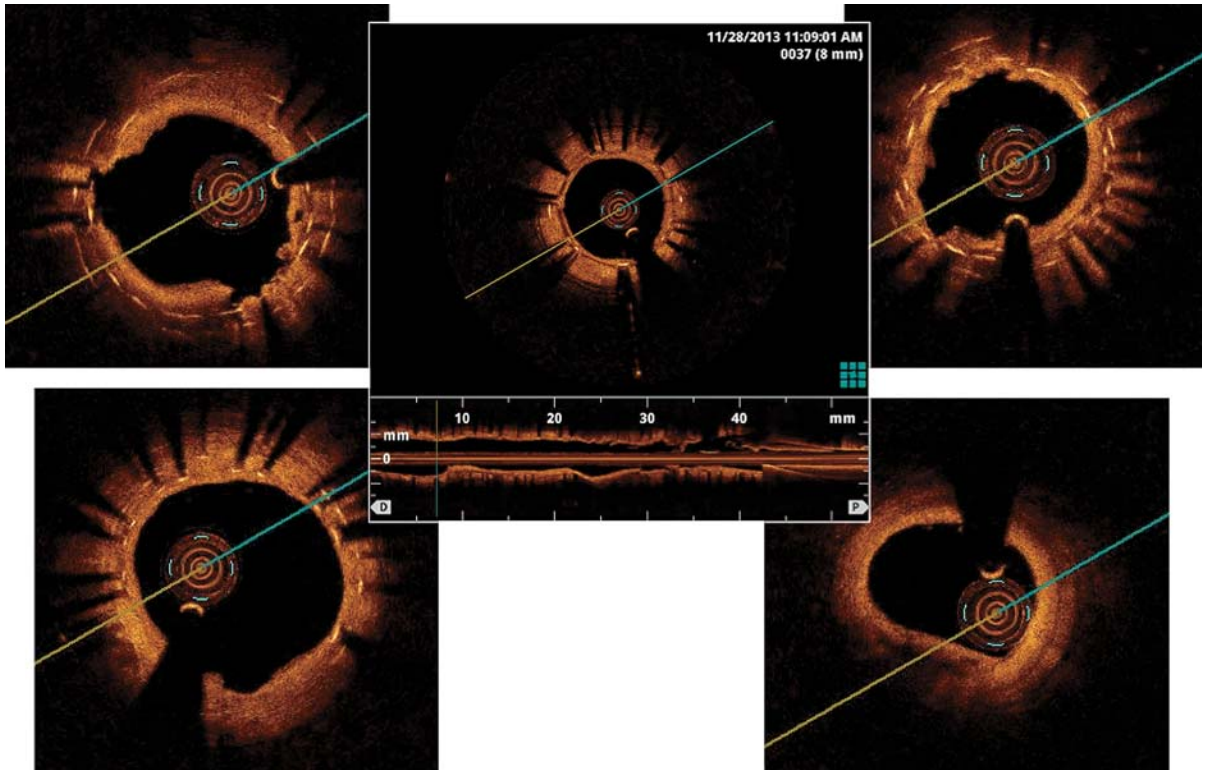

Figure 3. OCT after predilation using conventional coronary balloon. Good results are the basis for angioplasty with drug-eluting balloon. The patient was previously implanted with 3 layers of stents clearly visible on transverse sections.

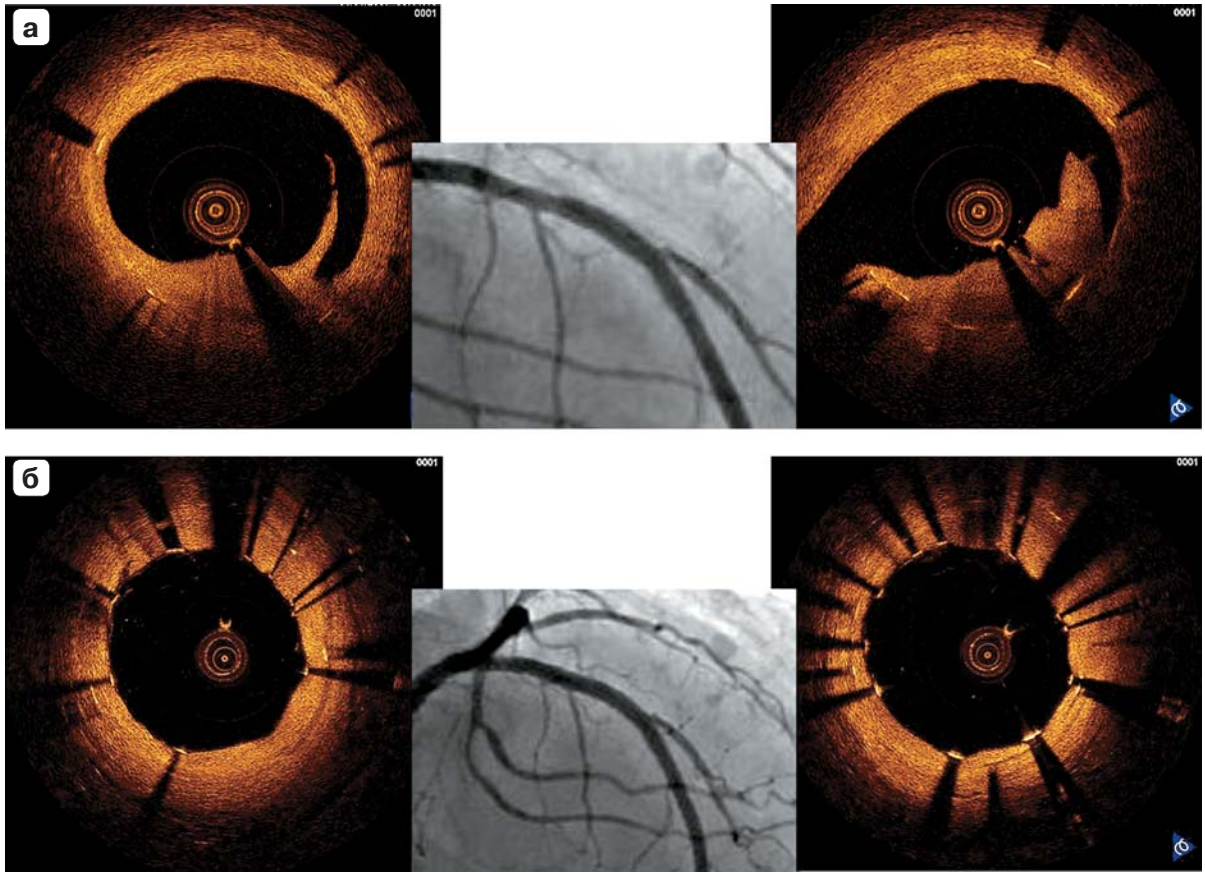

Figure 4. OCT after predilation using conventional coronary balloon.
A – severe dissection with thrombotic component is revealed, it is unreasonable to use the drug-eluting balloon.
B – optical and angiographic results after implantation of the drug-eluting stent.

were divided into three groups: satisfactory long-term outcome – 124 cases or 58.49% (74.25% of the control group), unsatisfactory long-term outcome in 43 cases or 20.28% (25.75% of the control group) and the third group included the patients who had no follow-up invasive procedures – 45 cases or 21.23% (29 patients or 13.68% were absent).

At follow-up, average stenosis degree by angiography was 40.37 ± 13.44% and 72.18 ± ± 21.76% in Group 1 and Group 2, respectively. The average stenosis degree by IVUS (43 cases) was 42.1 ± 7.3% in Group 1 (follow-up IVUS was not usually performed in Group 2). The stenosis degree by OCT (77 cases) was 53 ± 11.67%.

Intra-operational intravascular ultrasound was performed in 69 patients. The follow-up was performed in 66 patients after angioplasty using a drug-eluting balloon and 3 patients (after 2011 as OCT could not be used) after conventional coronary balloon use.

The intravascular ultrasound data obtained in 39 patients immediately after DEB angioplasty and follow-up were compared. The index of lumen loss averaged to 0.20 ± 0.06 mm, mean increase in the neointimal thickness was 0.12 ± 0.2 mm, the neointimal area at baseline and follow-up were 3.9 ± 2.01 mm^2 and 4.75 ± 2.22 mm^2, respectively. The negative index of lumen loss was observed in 6 cases; reduced thickness was noted in 7 cases and decreased neointimal area was found in 9 cases. It suggests that cell growth is actually inhibited by balloon-delivered drug.

195 OCT procedures were performed in 135 patients. This method was intraoperatively used in 119 patients for intermediate or final follow-up. During the intermediate follow-up, a severe dissection was revealed in 10 patients;

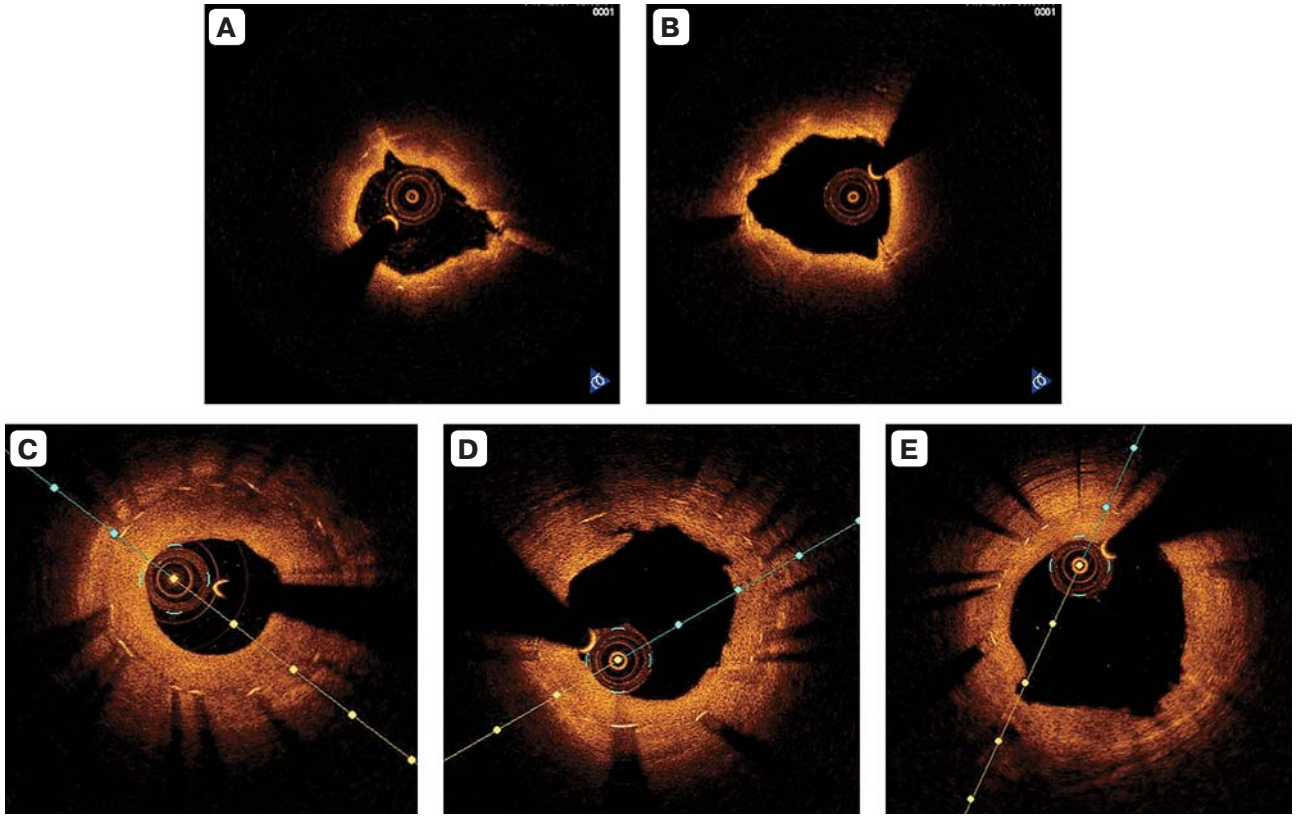

Figure 5. Additional measures in two patients after control OCT.
A – predilation with cutting balloon. The points of the blades exposure are clearly visible but the obtained lumen is insufficient.
B – after additional angioplasty with a balloon of larger diameter the satisfactory outcome was achieved, angioplasty with drug-eluting balloon was performed.
C – baseline OCT for in-stent restenosis. The stenosis area is 68%; the minimal diameter is 1.56 mm; the lumen area is 2.20 mm^2.
D – follow-upl OCT after angioplasty with balloon 3.0 × 14.0 mm. The angioplasty was insufficient. The stenosis area is 47.5 %; the minimal diameter is 2.44 mm; the lumen area is 4.68 mm^2.
E – OCT after additional angioplasty with balloon 3.5 × 14.0. The stenosis area was reduced to 32.2%; the minimal diameter was increased up to 2.65 mm; the lumen area was increased to 6.31 mm^2. Good predilation results, angioplasty using drug-eluting balloon was performed.

therefore, the drug-eluting balloons were not used and stents were required. The dissections were not angiographically severe in 5 of these cases (50%). Intermediate OCT was performed in 2 patients twice during intervention. The reason was that the angioplasty was not effective at the first follow-up (stenosis area of 60%, large neointimal area, insufficient residual luminal area). Additional angioplasty using a large balloon followed by OCT was performed (Fig. 5). The residual luminal area was increased and stenosis area was reduced to 45% in both cases.

OCT was performed in 110 patients to monitor the long-term results of DEB angioplasty (6 months after surgery). The OCT data obtained in 63 patients immediately after DEB angioplasty were compared with follow-up data. The index of lumen loss averaged to 0.10 ± 0.37 mm, mean increase in the neointimal thickness was 0.05 ± 0.22 mm; the neointimal area immediately after intervention and at follow-up was 3.88 ± 1.34 mm^2 (from 1.0 mm^2 to 7.27 mm^2) and 4.37 ± 1.65 mm^2 (from 1.63 mm^2 to 10.61 mm^2), respectively. Thus, the neointimal area increased by only 12.6% over 6 months indicating sufficient efficacy of the drug-eluting balloons for in-stent restenosis.

The negative index of lumen loss was observed in 19 cases; the reduced thickness and neointimal area were noted in 21 and 19 cases, respectively; it also demonstrates an actual inhibition of cell growth by the balloon-delivered drug (Fig. 6).

The long-term hemodynamically relevant lesions were found in 46 cases (21.7%). Repeated angioplasty using drug-eluting balloon

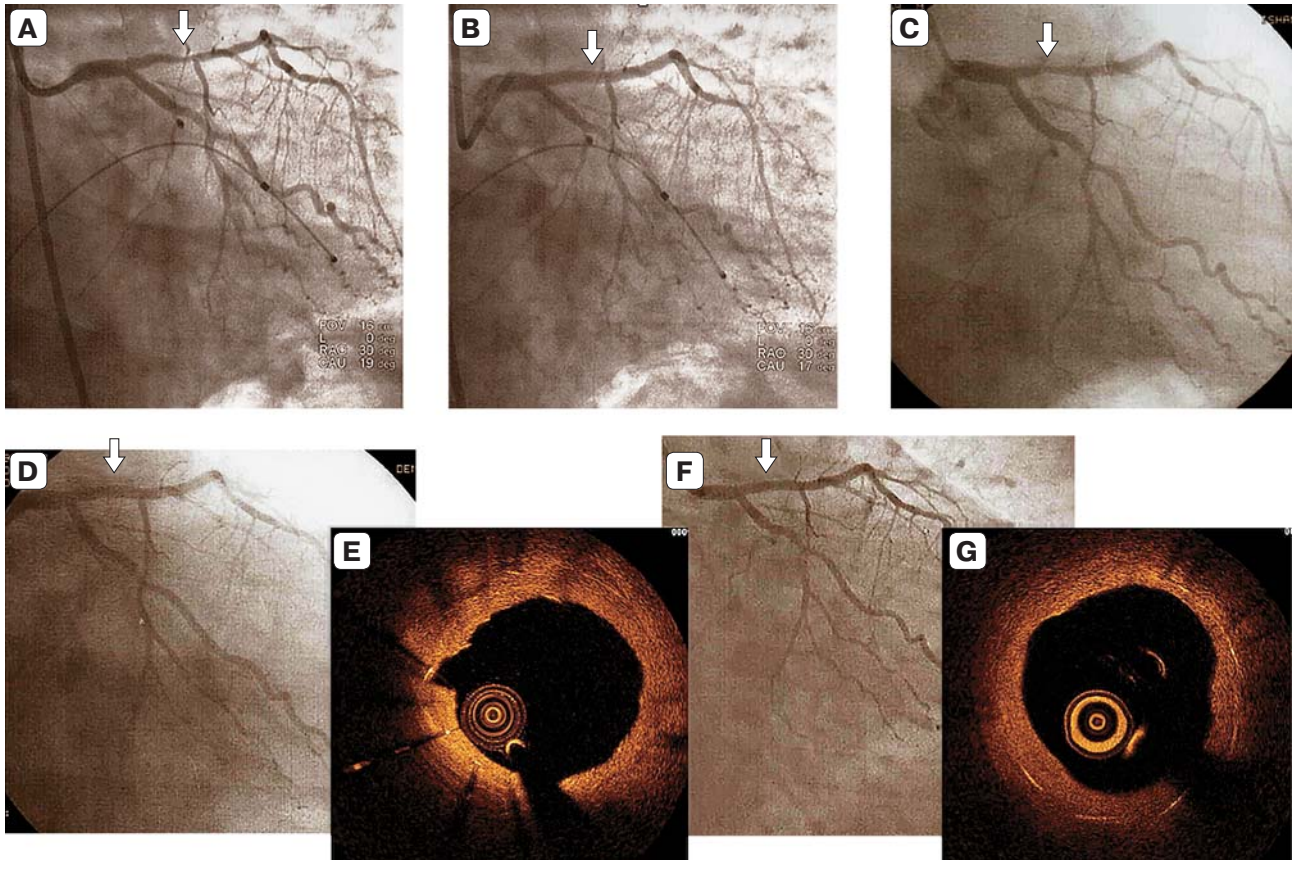

Figure 6. Immediate and long-term DEB results in a patient with LAD restenosis.
A – baseline angiogram of the initial lesion.
B – results of primary intervention: 2 stents were implanted from the LAD orifice (SatinFlex 3.5 × 25.0 and CC Flex 3.0 × 38.0).
C – restenosis in the proximal stent at Month 15.
D – results of angioplasty using balloon SeQuent Please 3.5 × 20.0, the residual stenosis is 20.64% based on angiography data.
E – follow-up OCT after angioplasty with drug-eluting balloon: the residual stenosis is 37.27 %, the intimal area is 4.76 mm^2.
F – follow-up OCT at Month 6, the residual stenosis is 20%.
G – follow-up OCT at Month 6, the residual stenosis is 35.41%, the index of lumen loss is negative –0.1 mm; thickness of the intima was increased by 0.02 mm, the intimal area was reduced to 4.71 mm^2.

and conventional coronary balloon was performed in 3 and 1 of these cases, respectively; drug-eluting stents were implanted in 38 cases; re-intervention was not performed due to diffuse distal lesions in 2 cases; two patients were transferred for CABG.

Discussion

The experience with drug-eluting balloons for in-stent restenosis on a regular basis, in our opinion, indicates the necessity for a differentiated and balanced approach to this treatment option. Although this treatment option is simple and friendly and requires no special clinical techniques, superficial approach to its implementation precludes from comprehensive discovering the potential of this method. Therefore, both compliance with the manufacturer's recommendations for balloon use and creative application of accumulated experience by the experts are of great importance.

In this respect, our experience with the intravascular imaging is quite demonstrative. IVUS and OCT were initially used to obtain precise quantitative data on the intervention results; however, with the accumulation of experience in analyzing these data, we decided to modify the approach and switch attention primarily to the predilation results prior to drug-eluting balloon. Due to exclusion of cases with non-optimal intima and lumen status after preliminary angioplasty, the actual advantages of the drug-eluting balloon can be used more efficiently with more complete and effective release of the drug substance. It should be noted that even distribution of drug substance over the intima is potentially one of the advantages of drug-eluting balloons, so it is highly important to achieve a sufficiently homogeneous surface after impact. Only intravascular imaging, especially optical coherence tomography with its high resolution, can confirm this result.

Another technological feature of the intervention which we have empirically discovered, serves the purpose of optimal delivery of the drug substance. To achieve a closer contact between balloon and vascular wall, and consequently, more complete delivery of the drug substance, in most cases we used the drug-eluting balloon with a diameter of 0.25–0.5 mm more than the initially implanted stent (after predilation with conventional coronary balloon with diameter equal to that of stent). We have usually used mean pressure for predilation (12 ± 2 atm) and nominal values for DEB angioplasty (8–10 atm).

We usually perform the systemic programmed follow-up angiography in the mid-term period – at Month 6 after DEB impact. The feasibility of such follow-up is related not only to objective assessment of treatment effectiveness but also to timely identification of possible repeated concerns in the intervened area in patients at high risk. Eventually, the repeated endovascular interventions were performed in 42 cases (91.3%) out of 46 cases when relevant re-stenoses were identified at follow-up, i.e. the secondary patency in the overall population was 98.1%.

The re-stenosis rate in our study after the drug-eluting balloons is 21.7%; it seems not too low at first glance. In real practice, we were unable to confirm the low rates of major cardiovascular events obtained in the above listed trials. We consider the drug-eluting stents to be more effective treatment option for in-stent restenosis in routine practice in terms of repeated revascularization rate. However, under appropriate conditions, it is advisable to postpone additional multilayer metallization of the stented segment. The cases as shown in Fig. 3, when there are 3–4 metal layers in the affected area would be a deadlock if there are no such devices as drug-eluting balloons. On the other hand, the re-stenosis rate is 50% after in-stent restenosis interventions with conventional coronary balloons. The above mentioned suggests that the drug-eluting balloons are essential component of equipment in the actively operating radiosurgical departments.

In conclusion, we present our modified recanalization technique with the use of drug-eluting balloons:

1. The diameter of the balloon for predilation should be consistent with the diameter of the previously implanted stent, and the diameter of the drug-eluting balloon should exceed the diameter of the previously implanted stent by 0.25-0.5 mm;

2. The inflation time is up to 1 minute but not less than 45 sec;

3. The drug-eluting balloon should be used over one segment only; to cover the entire length of the lesion, an additional balloon is recommended;

4. If several balloons are used, it is recommended to overlap them by at least 2 mm;

5. Follow-up OCT (preferable) or IVUS after proper predilation using a conventional balloon is recommended to assess the efficacy of angioplasty and make a decision on subsequent application of the drug-eluting balloon or stent;

6. 6-month follow-up coronary angiography followed by OCT or IVUS is appropriate to evaluate the long-term outcome and make a timely decision on a possible additional impact.

Conclusion

Angioplasty using drug-eluting balloons expands the endovascular treatment options for intracoronary stent restenosis. It is important that the drug-eluting balloons require no fundamental changes of interventional technique and do not complicate the intervention. Meanwhile, proper use of drug-eluting balloons and preparation of a vessel for this specific balloon are of great importance to achieve favourable immediate and long-term outcomes. IVUS and OCT used for intraoperative qualitative and quantitative control of DEB-related interventions increase the efficacy of these interventions, prevent intraoperative complications, and reliably evaluate the long-term results. The drug-eluting balloons are not associated with any specific complications during intervention and long-tong period.

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Intravascular Ultrasound Scanning for Measurement of Patent Ductus Arteriosus

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The routine experience of intravascular ultrasound scanning in patients with the patent ductus arteriosus is summarized. IVUS was performed in 56.3% of intervened patients excluding only those with small diameter PDA. 234 procedures were performed in the intervened patients and 31 procedures – at the diagnostic stage only. For the first time, 3 types of PDA structures as well as such morphological features as pulsation, oval or irregular shape were identified based on IVUS data. Ultrasound measurements of ductus arteriosus significantly exceeded angiographic measurements. The sizes and type of tools for PDA closure were selected according to the proposed algorithm based on IVUS data.

Keywords: *patent ductus arteriosus, intravascular ultrasound, endovascular treatment of PDA.*

Objective. To demonstrate the possibilities of intravascular ultrasound for measurement of quantitative parameters and qualitative characteristics of the patent ductus arteriosus as well as IVUS data to be used in endovascular treatment of PDA.

Methods. IVUS was performed in 265 patients examined and treated for PDA. 234 of them underwent endovascular ductus closure and 31 patients were examined at the diagnostic stage. IVUS was performed in 56.3% of all patients intervened for this abnormality.

Results. The qualitative analysis of intravascular ultrasound images of PDA revealed several types of its wall visualization and 3 types of the arterial duct were identified. Type 1, 2, and 3 ducts were found in 54.5%, 27.3%, and 18.2% cases, respectively. Additionally, the morphological features of the arterial duct able to affect the treatment results were determined: PDA wall pulsation (24.2% of cases), oval (44.4%) and irregular (31.3%) shape. Totally, the various ductus types different from the concentric ones were observed in 60.7% of patients. When quantitative results of angiography and IVUS were compared, the minimal ductal diameter was 26% more based on IVUS than based on angiography. The same results were obtained concerning the PDA smallest cross-sectional area. However, both the minimal diameter and cross-sectional area of the ductal ampulla were similar and had no significant differences.

Conclusions. IVUS is able to measure the patent ductus arteriosus more precisely compared to angiography. Moreover, IVUS identifies different types and anatomical features of the PDA which cannot be fundamentally detected by angiography. IVUS helps to select the required type and size of tools for endovascular intervention more adequately and optimize its results.

Introduction

The development of interventional treatments has made them the main modalities to correct such a widespread congenital disease like patent ductus arteriosus (PDA). The efficacy and safety of endovascular interventions are directly dependent on the accuracy of preoperative diagnosis and thoroughness of morphometric measurements. The limitation related to the ductal size is currently not relevant because Amplatzer occluder devices and similar devices have been developed. Nevertheless, precise measurement of the ductal diameter is still very important for selection both the type and size of the occluder device, especially when the angiographic measurement is difficult due to overlapping vascular structures or severe angulation of the area of interest (1–3).

In the article concerning IVUS in congenital heart defects, F. Ricou et al., 1991 were the first to report the possibility of intravascular ultrasound scanning for patent ductus arteriosus

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(1). Most publications report isolated cases of intravascular ultrasound for PAD including measurement of the ductal diameter (4, 5), selection of the treatment option, i.e. surgical or endovascular (6), qualitative assessment of the morphology of the arterial duct (6, 7).

The only study to analyze a relatively large number of IVUS procedures in endovascular occlusion of patent ductus arteriosus was that of Z.M. Hijazi et al. (8). This article compared IVUS with angiography in 26 patients. The authors used intravascular ultrasound not only to measure PDA diameter but to assess the degree of spiral protrusion in the aorta. The mean age of patients was 1.7 years (from 2 months to 34 y.o.). The following probes were used in the study: 30 MHz/3.5 F and 20 MHz/4.8 F. The authors assumed a possible influence of the probe itself on the ductal lumen based on its sufficiently large diameter compared to modern probes. The authors have found a strong correlation between angiographic and ultrasound measurements. However, the average diameter measured by IVUS was 0.4 mm greater than measured by angiography; the difference was 0.5–0.9 mm in 42% of patients. Nevertheless, it was concluded that IVUS should not be used routinely to measure patent ductus arteriosus, and that greater accuracy of angiographic data could not be excluded.

Another recent publication on intravascular imaging techniques for PDA should be mentioned (9). This study presents the first two cases when optical coherence tomography was used for diagnosis of patent ductus arteriosus. The correct displaying of the arterial duct including its 3D reconstruction and accurate sizing proved to be possible. Although the measured sizes differed (they were greater according to the OCT data) and this was potentially significant for selection of devices parameters, the ductus in patients was closed based on the angiographic measurements.

Although intravascular visualization options have a potential in this congenital defect, they are not actually used in real practice. Therefore, presentation of our clinical experience with IVUS for PDA measurements is even more relevant.

Materials and methods

The endovascular interventions in patients with patent ductus arteriosus are performed in the Department of Endovascular Methods of Diagnosis and Treatment of Orenburg Regional Hospital since 2000. By the end of 2015, 416 endovascular closures of PDA using the following devices were performed: Flipper PDA detachable embolization coils (330 cases), Prokubovskiy's Botallooccluder (2 cases), Nit-Occlud PDA occlusion system (25 cases), Amplatzer occluder devices and its analogues (Cera, HeartR, PDA-R) (59 cases). Although digital angiographic systems were used for morphometric measurements, the first procedures showed that angiography not always gave the precise results. Transthoracic echocardiography gives even less accurate information on the ductal sizes. Visualized shunts have different shapes and not always allow PAD identification. Therefore, the echocardiography can be used for screening and identification of shunts but not for quantitative measurements. By 2000, we had some experience in intravascular ultrasound in various vascular regions and attempted to use this method for PDA measurement. Naturally, our priority was not the ability to visualize the vascular wall components but rather precise direct measurements of the anatomical vascular formations: smallest diameter of the patent ductus arteriosus and its ampulla. The informative value of the obtained data was confirmed in our first procedures (2, 10, 11) and contributed to currently routine use of the intravascular ultrasound for PDA closure in our Department.

265 intravascular ultrasounds of the patent ductus arteriosus were performed. 31 procedures out of them were performed at the diagnostic stage; further endovascular interventions were not performed for various reasons. Most procedures were performed in the time period when modern occluders were not available and large diameter of the arterial duct was a contraindication for radioendovascular treatment. The remaining 234 procedures were performed when endovascular closure of PDA was done simultaneously or at the second stage. Thus, IVUS was performed for 56.3% of the intervened patients. IVUS was not performed for small diameter ductus (comparable or smaller than the size of the diagnostic catheter; in some of these cases, the ductus predilation was required using a coronary balloon 1.5–2 mm to introduce a delivery system).

Intravascular ultrasound was performed using three generations of EndoSonics/Jomed/Volcano devices – Oracle, In-Vision Plus, s5/s5i. All devices use 20 MHz phase-electronic probes. Manual probe pullback was carried out during procedures. When an image of the patent ductus arteriosus was analyzed and processed, its diameter and the lumen area were

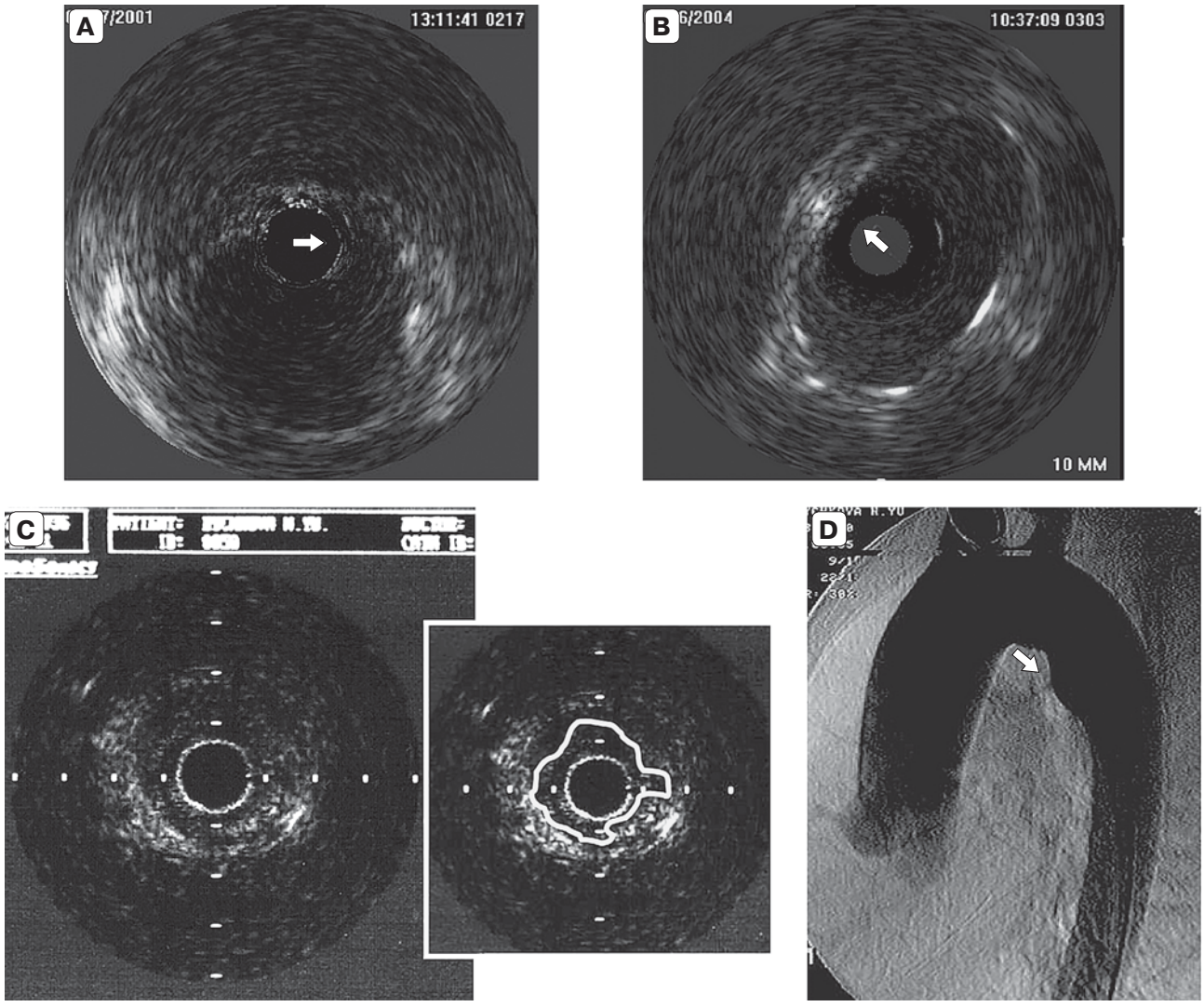

Figure 1. Type I patent ductus arteriosus. A, B – different variants of IVUS images of the type 1 PDA; C – IVUS of the recanalized type 1 PDA after surgical ligation; D – angiogram of the same patient.

measured at two or three segments; the diameter and the lumen area of the ampulla, if pronounced, were also measured. These measurements were compared with angiography results.

In 100 cases (37.7%), the third longitudinal projection of the ductus could be reconstructed based on the intravascular ultrasound data.

The female patients prevailed (70.7%). Quite large numbers of older children and even adults were specific for our population. The mean age of children was 7.93 ± 4.42 y.o.; the mean age of patients older than 18 y.o. was 32.61 ± 11.55; the mean age of all patients was 12.79 ± 1.77 (from 2.5 to 53) y.o.

Results

Analysis of morphological types of PDA

Despite a primary attention to morphometric measurements via intravascular ultrasound, we have identified previously not described qualitative features of the PDA morphology which may be of clinical significance. The qualitative analysis of intravascular ultrasound of the patent ductus arteriosus identified several types of its wall visualization; hence, 3 types of the arterial duct were determined.

The first type (the most common, especially in children) is characterized with thin or uneven wall without a clearly distinguishable internal structure (Fig. 1, A, B). The lumen may be irregular, as often occurs in case of recanalization after surgical ligation (Fig. 1 C, D). In our study, this type of the patent ductus arteriosus was found in 54.5% of cases.

Type 2 of the ductus is characterized with echo un-enhanced wall and its limits are difficult or impossible to determine on one frame without repeated dynamic view of completed recording (Fig. 2). This type is especially common in case of a large diameter ductus

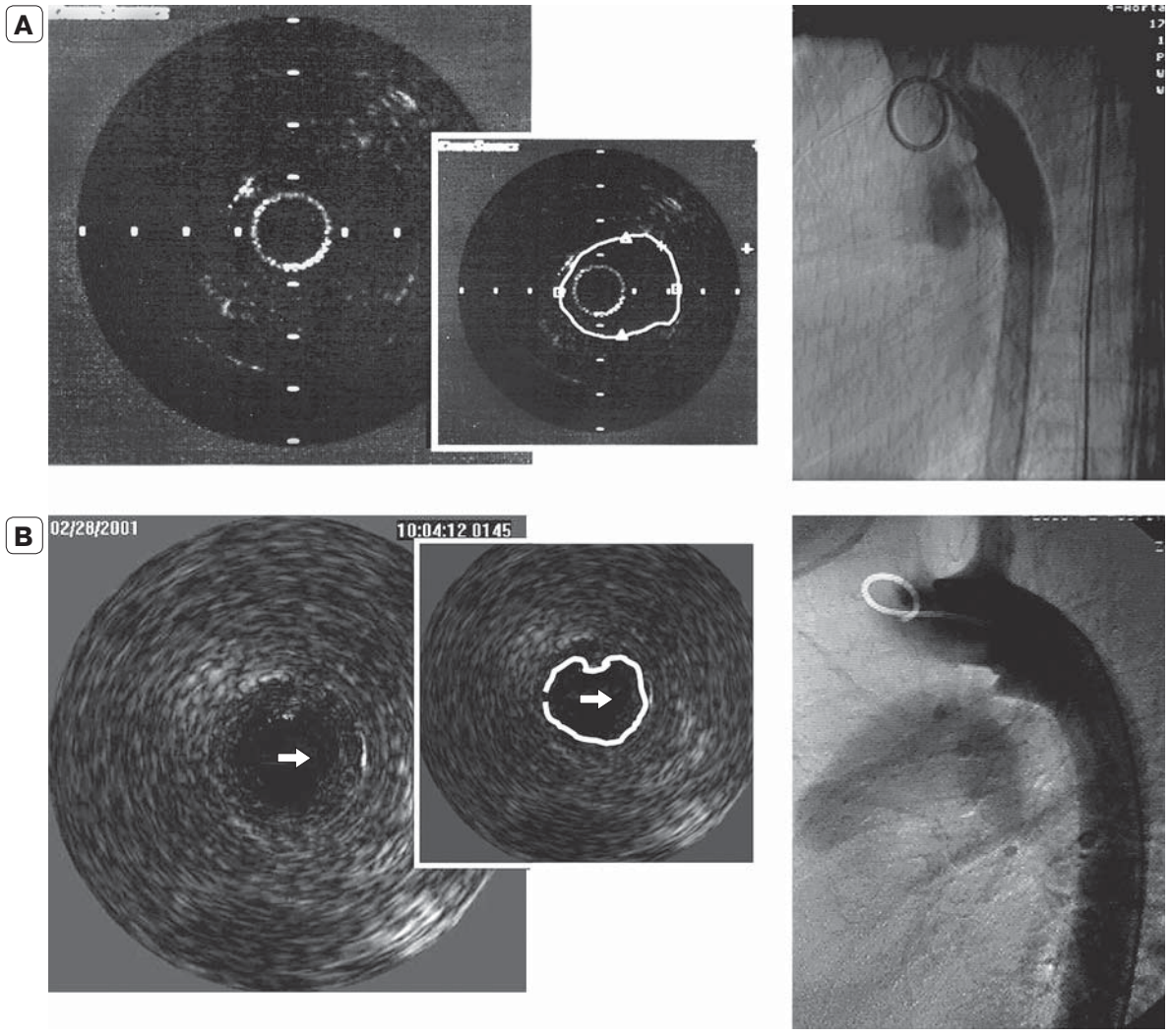

Figure 2. A, B – different variants of IVUS and angiographic images of the type 2 PDA.

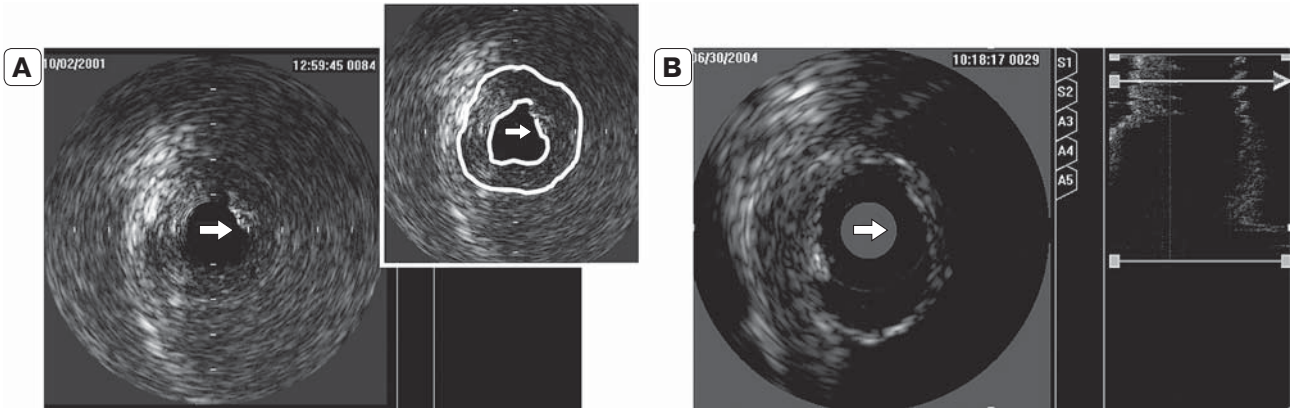

Figure 3. A, B – different variants of IVUS images of the type 3 PDA.

(>45mm). This very type prevailed in the above mentioned diagnostic population not eligible for endovascular intervention without modern occluders. 27.3% of all patients had type 2 ductus.

The third type is typical for adult patients: the ductal wall is clearly visualized around the perimeter and sometimes slightly thickened. In some cases, the ductal wall may have a multilayer structure (Fig. 3). In Type 3, the longitudi-

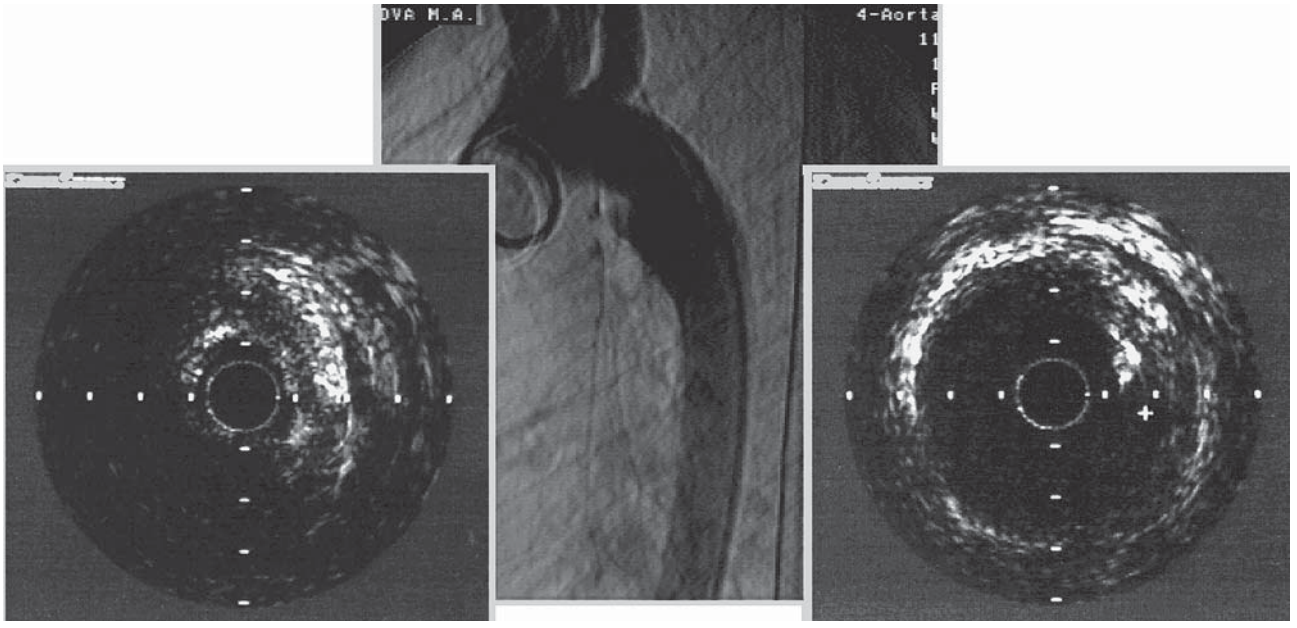

Figure 4. Pulsatile PDA with pronounced difference between the systolic and diastolic diameters.

nal ultrasound projection of the ductus is usually possible to reconstruct as opposed to other types. This type of ductal structure was observed in 18.2% of cases.

In addition to identification of three types, IVUS determined a number of ductal features fundamentally indistinguishable by angiography, which can directly influence endovascular treatment results and contribute to unsatisfactory outcomes.

Ductal wall pulsation is one of these features. In some cases, it is very pronounced and significantly changes diameter and cross-sectional area of the ductus on various frames in systole and diastole when a probe is fixed. For small PDA, this phenomenon does not significantly affect the intervention requiring only increased attention at the stage of coil detachment. If the ductus is large, the tool sizing based on the smallest diameter of the lumen without considering pulse fluctuations can lead to coil displacement, fluctuations or incomplete PDA closure (Fig. 4). The ductus was considered pulsating if based on IVUS data the smallest diameter changed by >10% between systole and diastole. The pulsating PDA was frequently observed in patients when IVUS was performed (24.2%). The mean differences between the diameters and areas in these patients were 11% and 20%, respectively.

Another feature of the PDA, observable only with intravascular ultrasound, is its oval elongated form in cross section (Fig. 5, A). Angiographically measured diameter in this type of the ductus is often similar to the smallest diameter measured by IVUS. However, the elongated shape of the PDA means a corresponding increase in the cross sectional area that, at best, can result in incomplete elimination of abnormal shunt and, at worst, to coil shifting due to unstable fixation. For quantification of ductal eccentricity, we calculated the largest / smallest PDA diameters ratio on the smallest cross-sectional area. The highest ratio was 1.83. 44.4% of patients had eccentric ductus (the ratio >1.2). The mean ratio was 1.19 ± 0.02. It should be noted that during procedure and data analysis, probe inclination relative to the longitudinal axis of the ductus is to be avoided. Otherwise, the judgment on possible oval shape of the ductus may be unreliable.

In some cases, the patent ductus arteriosus had irregular shape, sometimes very pronounced, in a cross section. It was frequently associated with the previous surgical ligation. Sometimes this feature, considerably important for the endovascular intervention outcomes, was observed in previously non-intervened patients (Fig. 5, B-D). The irregularly shaped ducti were often observed (21.3% of cases).

As the above mentioned anatomical types can be found not only as isolated types but in various combinations, the ducti with various shapes other than concentric ones were observed in 60.7% of patients. Thus, in most patients routinely undergoing interventions based on the angiographic results only, the operator

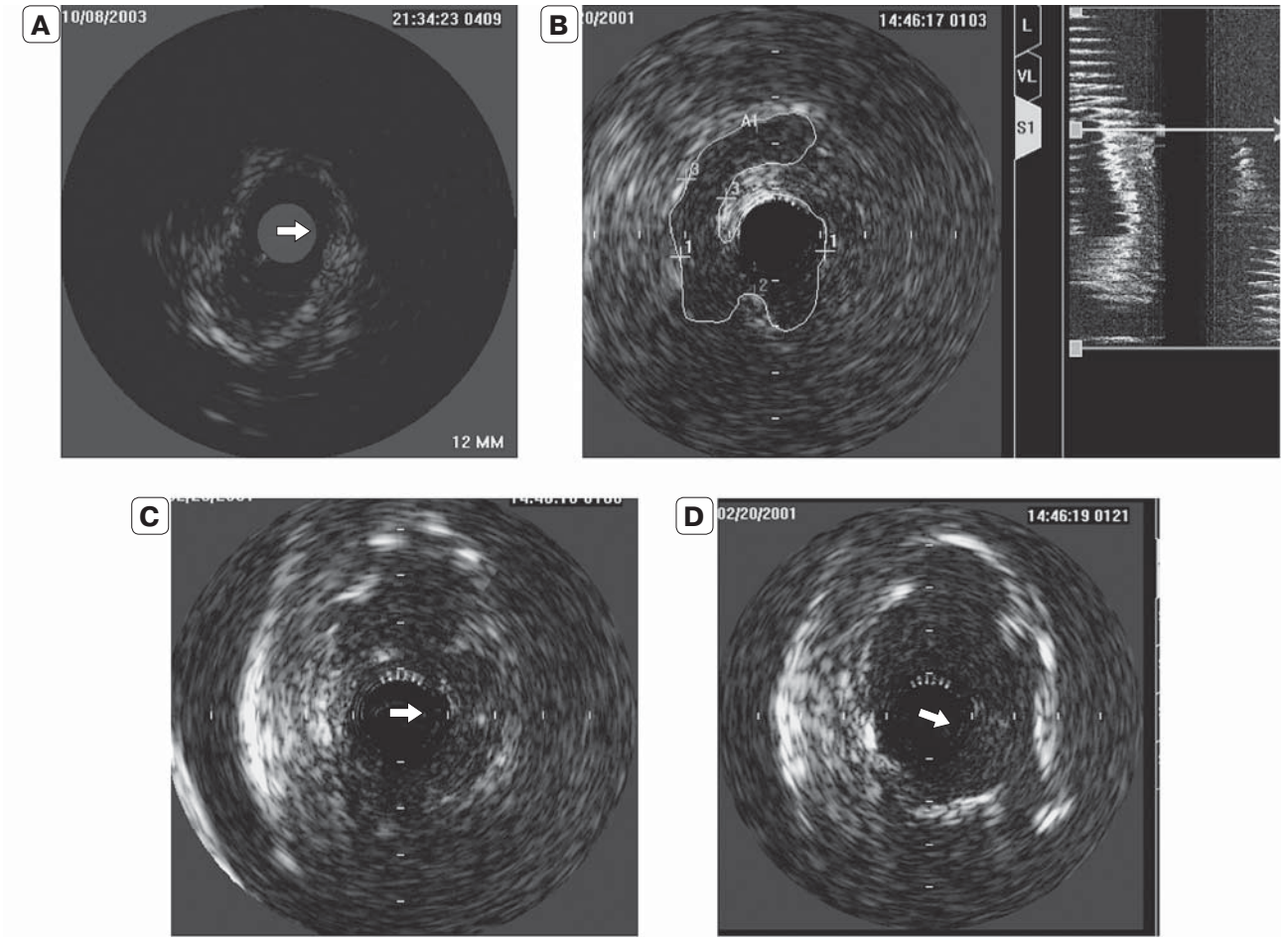

Figure 5. A – oval PDA; B–D – various segments of irregularly shaped PDA.

has no information on true shape of the ductus which can affect the endovascular intervention results.

Ivus for endovascular closure of PDA

The feasibility of intravascular ultrasound for quantitative morphometric measurements prior to intervention is associated with direct reliable visualization of the vascular wall and intraluminal structures in contrast to angiography and transthoracic echography when only blood flow or enhanced "snapshot" of the vessel is visible.

The comparison of quantitative measurements provided by angiography and IVUS (Table 1) showed that the smallest diameter of the ductus measured by ultrasound scanning was significantly higher than those measured by angiography (by 26%). However, the largest diameter in the same cross section differed even more exceeding the angiographic size almost 1.5-fold. The same applied to the smallest cross-sectional area of the PDA. Meanwhile, both the smallest diameter and cross sectional area of the ductal ampulla were similar and had no significant differences.

The individual data of the smallest ductal diameter measured by angiography and IVUS were identical (difference was less than 0.1 mm) in 22.2% of cases only. The diameter was larger based on the IVUS data (maximum dif-

Morphometric measurements of the patent ductus arteriosus

	IVUS	Angiography	p
Min LD of the arterial duct, mm	2.87 ± 1.15	2.27 ± 1.56	<0.001
Max LD* of the arterial duct, mm	3.45 ± 1.37	2.27 ± 1.56	<0.001
Ductal LA, mm^2	8.21 ± 7.45	4.37 ± 5.85	<0.001
Min LD of the ampulla, mm	4.45 ± 1.25	4.69 ± 2.32	0.467
Ampullary LA, mm^2	18.92 ± 10.13	15.66 ± 11.80	0.162

* Max LD is the largest diameter in the smallest cross-sectional area (in contrast to Min LD which is the smallest diameter in the same area).

ference of 2.24 mm) in most cases (62.1%) and in 15.5% of cases based on the angiography data (maximum difference of 5.7 mm). Importantly, it was impossible to measure PDA diameter using angiography in 10 cases when the ductus was short. The lumen area was larger based on intravascular ultrasound in 65.5% of cases and in 25.5% based on angiography, the results were identical only in 5 cases (9.1%). It seems especially important that in 110 patients (41.5%) the measurements differed so much that directly affected the treatment tactics and tools of different size or even type were to be selected. In most of these cases (77.1%), coil or larger occluder was preferable according to the IVUS data.

Based on these measurements, 234 patients underwent endovascular closure of the ductus. Among intervened patients, 57.6% had anatomical type A1 according to the classification proposed by A. Krichenko et al. (12), 16.3% – type A2, 3.3 % – type B1, 8.2 % – type B2, 1.1% – type B3, 6.5 % – type C, 6.5 % – type D, 0.5 % – type E. The mean pulmonary artery pressure was 33.23 ± 1.70/15.24 ± 1.70 mm Hg.

Given the possibility of accurate measurement of the ductus and evaluation of its morphology, as well as development of various tools for PDA closure, we use the differential approach to selection of various devices based on the data obtained using intravascular ultrasound. Till 2004, inclusively, the spectrum of available tools was limited and the following tactics was used: concentric ductus <3.5 mm in diameter was embolized with a coil (one coil with extra coil if severe residual shunt persisted); concentric ductus from 3.5 to 4 mm in diameter or oval or irregularly shaped ductus from 3 to 4 mm in diameter was closed with programmed embolization using two coils; ductus >4 mm in diameter was surgically closed. Since 2005, this tactics was modified as follows: concentric ductus <2.5 mm in diameter is closed by coil embolization; concentric ductus from 2.5 to 3.5 mm in diameter or oval or irregularly shaped ductus from 2 to 3 mm in diameter is embolized with a coil occluder (NitOcclud); concentric PDA > 3.5 mm in diameter or oval or irregularly shaped ductus > 3 mm in diameter is closed with Amplatzer occluder devices or similar device.

Before intravascular ultrasound was introduced, one coil displacement in the distal branches of the pulmonary artery was noted per 7 interventions (14.3%). When IVUS was introduced, no coil displacement or embolization-related complications were observed in the analyzed population due to adequate sizing of the tools.

The complete closure of the ductus was immediately achieved on the operating table in 85.5% of patients. Echocardiography demonstrated complete shunt elimination 3–4 days after intervention in 10 more patients (4.3%, mainly patients with implanted occluder devices). However, on the contrary, the echocardiography within this time frame more frequently revealed a residual shunt after the ductus was angiographically closed. By echocardiography, the residual shunt persisted in 20.9% of patients upon discharge. Most of these cases were observed when only coil embolization was used; large coils or two coils were implanted in 58.8% of these cases. In most cases, follow-up echocardiography revealed complete ductus closure within 3–12 months. The residual shunt persisted for 9–12 months in 17 patients (7.3%). 12 out of these patients underwent additional coil embolization and the ductus was completely closed in 9 cases. In two additional cases, the extra coil was not implanted due to technical difficulties in introducing the delivery system; however, the ductus was closed after these manipulations. In one patient, re-embolization failed due to the small size and tortuosity of the residual hole, precluding from introducing the delivery system. Additional radioendovascular intervention was not performed in two patients previously implanted with Botalloocculder. Finally, in three cases after supplemented embolizations the residual shunt was significantly reduced but not eliminated completely. Two of these patients were eventually implanted with three coils each (one patient – two coils at baseline and one extra coil and another patient – two additional embolizations), a third female patient of 51 y.o. was implanted with 4 coils in 3 steps.

When the ductal types and morphological features were analyzed in patients with residual shunts, no marked differences were noted compared to the overall population. There were slightly more patients with type 2 ductus (33.3% when residual shunt was observed via angiography and 31% when echocardiography was used) and irregularly shaped ductus (42.9% and 39.4%, respectively). However, the patients who required considering re-intervention in later terms after primary intervention, had morphological differences from the overall population. There were fewer patients with types 1

(41.2%) and 2 (11.8%) and more patients with type 3 (47.1%). Moreover, there were more patients with irregularly shaped ductus (29.8%) and pulsating ductus (41.2%); any morphological feature or its combination was observed in 76.5% of patients.

Thus, the ductus with formed thickened irregular wall or pulsating ductus are the factors contributing to incomplete closure of PDA after initial embolization.

Discussion

Even modern digital angiography with quantitative measurements not always provides accurate and reproducible results in evaluation of the patent ductus arteriosus, which strongly depend on parameters of contrast injection, calibration accuracy, and limitations of the angiography technique. Transthoracic and transesophageal echocardiography provides even less accurate quantitative data in this disease.

Intravascular imaging seems to be natural and logical solution to this problem. Nevertheless, this method is described only in a few articles. It is partly explained by the fact that approximate results obtained using angiography are sufficient to achieve satisfactory outcomes of endovascular interventions. Both Z.M. Hijazi et al., 1998 (8) presenting the widest experience in IVUS-guided assessment of PDA by then, and J. A. Hill et al. 2015 (9) showing OCT potential in ductus assessments, demonstrate that the intravascular visualization options provide more precise information compared to angiography, and the ductal sizes with intravascular imaging are significantly bigger. Z.M. Hijazi et al. did not rule out a role of IVUS catheters, which had a quite large profile at that time, in affecting accuracy of PDA measurements. Quite low profile of modern catheters eliminates such influence. We absolutely preferred IVUS data over angiography and larger tools were selected in more than 40% of cases based on the IVUS results. Non-complicated interventions with positive clinical results demonstrate the accuracy and reliability of measurements and chosen criteria for tools selection. The absolute advantage of IVUS is the ability to measure the PDA when angiographic measurements are impossible, e.g., for very short ductus and atypical orifice or ductus overlapped by the aorta.

Based on the presented sizes, both ducti in the study of J.A. Hill et al. had an oval shape. However, we did not find any mention on morphological types and characteristics of the patent ductus arteriosus in the available literature.

In our opinion, the types of PDA presented in this study demonstrate the capabilities of intravascular imaging for in vivo assessment of biological structures. According to our data, the described types of the ductal wall structure are not solely anatomical, but have clinical significance. It should be noted that the ductus with better visible and usually more dense wall, especially for large diameters, are often not occluded immediately after embolization, and some patients ultimately require implantation of extra coil. Thus, this type of PDA detected by IVUS requires continued intervention until complete closure of the ductus. Identification of oval ductus requires a careful approach for it is naturally accompanied by an increase of the cross sectional area and, consequently, jeopardizes reliability of abnormal shunt elimination. Finally, the irregular shape of the ductus in a cross section can imply possible multifenestrated structure which also worsens the embolization outcome. Potential construction of the third projection in case of patent ductus arteriosus does not give significant additional information: a resulting picture is similar to angiographic one, however, sometimes helps to identify the narrowest place of the ductus.

Conclusion

The presented data indicate that intravascular ultrasound is able to measure the sizes of patent ductus arteriosus more accurately compared to angiography. Moreover, IVUS identifies different types and anatomical features of the PDA which are not fundamentally detected by angiography. Intravascular ultrasound in congenital heart defects is a safe and informative diagnostic tool. Due to these IVUS-related advantages, the required tool type and size for endovascular intervention can be selected more adequately, thus optimizing its results.

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Immediate and Early Results of a Clinical Trial Comparing Different Strategies of Drug-Eluting Stents Implantation Under IVUS or Angiographic Guidance

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We present immediate and early (one month) results of a single-centered randomized trial "ORENBURG" comparing different strategies of drug-eluting stents implantation under IVUS and angiographic guidance. The trial comprised 1032 patients; among them, 676 were operated under IVUS guidance and 356 – under angiographic guidance, with similar distribution of 6 types of "limus"-eluting stents. Immediate in-hospital results were marked by a very low incidence of MACE – 0.1% (0% in the subgroup of IVUS, 0.28% in the subgroup of angiography). Within one month after the procedure no additional adverse events were noted.

Keywords: *intravascular ultrasound study, coronary stenting, intravascular imaging, optical coherence tomography, angiography, drug-eluting stents.*

Purpose. To present immediate and early (one-month) results of a single-centered randomized controlled prospective trial comparing different strategies of drug-eluting stents implantation under the guidance of IVUS or angiography ("ORENBURG").

Methods. The trial comprised patients with native coronary arterial lesions, who received "limus"-eluting stents of six types. After randomization by the type of stents, the patients were randomized to the subgroups with 2 : 1 ratio according to the type of guidance used during the operation – ultrasound or angiography. In case of discordance with the special ultrasound criteria of optimal stenting, an additional repair with repeated IVUS guidance was performed. At the final stage of the operation the patients from both subgroups underwent optical coherence tomography, however independently of its results no additional intervention was performed.

Results. Among 1032 patients, 676 were operated under IVUS guidance, and 356 – under quantitative angiography guidance, with even distribution by the types of implanted stents. In the subgroup of IVUS the severity of the target lesion was somewhat higher due to more numerous "left main" and bifurcation lesions. Immediate in-hospital results were marked by a low incidence of major cardiovascular events – 0.1% (0% in the subgroup of IVUS, 0,28% in the subgroup of angiography). Within one month after the procedure no additional adverse events were noted. In cases, where direct comparison of different imaging methods data was feasible, significant differences were noted practically in all pairs of indices, with moderate positive correlation. The absolute values of the measured parameters rose in the series "Angiography – OCT – IVUS" for all the indices, except for minimal lumen diameter.

Conclusions. Immediate and early results of "ORENBURG" trial were characterized by a very low incidence of adverse events in both subgroups of patients. The dynamic evaluation of the patients' condition, including angiography and OCT in 6 months and 2 years after the operation, should allow to make more objective conclusion concerning the role of IVUS for the improvement of the results of DES implantation.

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Introduction

The methods of intravascular imaging, firstly – intravascular ultrasound, had accompanied coronary stenting at all stages of its development. The introduction of drug-eluting stents (DES) not only improved the long-term results of stenting, but also marked the apparition of some specific problems, which, finally, contributed to the increased significance of intravascular imaging methods at a new level.

The use of intravascular ultrasonic scanning during coronary interventions became a routine practice in the Department of Endovascular Methods of Diagnosis and Treatment of the Orenburg regional hospital from the first years of its activities. Already in 2005, we classified the implantation of DES as one of the "specific cases of stenting" requiring priority use of intravascular ultrasound (1).

Several Registries and large meta-analyses comprising up to 26500 patients (2–9) suggest the benefits of using intravascular ultrasound during the implantation of DES. However, until recently no large randomized trials comparing DES implantation under the guidance of angiography and IVUS have been presented. In 2012, when we decided to conduct this study no such publications were available. As we had a certain experience with the use of intravascular ultrasound in coronary pathology, we decided to compare the strategies of stenting under the guidance of angiography or IVUS in a rather large cohort of patients, using a full-value randomization without strict limitation of inclusion criteria, in order to maximally approach our sampling to the real practice.

In 2015, the results of a multicenter trial IVUS-XPL (10) comprising 1400 patients from 20 Korean hospitals were published; it became the first full-value randomized comparison of the strategies of coronary interventions performed under IVUS or angiographic guidance in the era of DES. The trial demonstrated a significant decrease of the rate of major cardiovascular events within one year in the IVUS subgroup, mainly due to the decrease of the number of repeated revascularization.

Deficient number (and until recently – complete lack) of randomized trials on the above problem remains the main cause of an insufficiently high class of recommendations and evidence level for the use of intravascular imaging in everyday clinical practice. This fact confirms the relevancy of our work.

Material and methods

A clinical trial comparing the strategies of drug-eluting stents implantation under the guidance of IVUS or angiography – the single-centered randomized controlled prospective trial "ORENBURG" ("Optimal DES implantation under joint guidance of IVUS and optical coherence tomography") – was started in 2012, on the base of the Department of Endovascular Methods of Diagnosis and Treatment of the Orenburg regional hospital. The trial is registered at the Website ClinicalTrials.gov (ID NCT01917201), the protocol of the trial was adopted by local ethic committee.

The patients received 6 types of "limus"-eluting stents, which were the best studied by the time of the start of the trial: Xience Prime / Xience V, Promus Element, Resolute Integrity, Biomatrix Flex, Nobori, Orsiro. The trial comprised 1032 patients, who were primarily randomized according to the type of the stent implanted, and then – by the type of guidance used during the intervention (IVUS or angiography), at a 2:1 ratio. The inclusion criteria were sufficiently broad and involved lesions of the native coronary arteries not longer than 60 mm (coverable by two stents maximally) in the vessels with the diameter of at least 2.75 mm.

Balloon angioplasty and stenting were performed in accordance with the standard technique.

Intraoperative anticoagulation and postoperative antiplatelet therapy were conducted in usual dosages. In the subgroup of IVUS, the intravascular study was performed at the initial stage of the intervention for the determination of the parameters of stenting, as well as during the final stage, in order to confirm that the results were compatible with the criteria of optimal implantation. If these criteria were not reached, repeated IVUS was performed after additional manipulations. After the end of the intervention, control optical coherence tomography was performed in both subgroups. After that, independently of the results, no additional manipulations were considered.

The design, the schedule and the end-points of the study, technical particularities of IVUS and OCT, as well as the IVUS-based criteria of optimal stenting developed for this trial, have been described earlier (11).

The obtained results were statistically processed using statistical software SPSS Statistics v. 23 (IBM, USA) и Statistica v.6.1 (Stat Soft, USA).

Table 1. Patients' data

Parameter	Total (n = 1032)	IVUS subgroup (n = 676)	Angiography subgroup (n = 356)	p_{3-4}
1	2	3	4	5
Age, years	56.69 ± 8.02	56.81 ± 8.30	56.47 ± 7.48	0.504
Sex:				
M	856 (82.9%)	562 (83.1%)	294 (82.6%)	0.945
F	176 (17.1%)	114 (16.9%)	62 (17.4%)	0.851
Diabetes mellitus	162 (15.7%)	97 (14.3%)	65 (18.3%)	0.163
Obesity	215 (20.8%)	144 (21.3%)	72 (20.2%)	0.743
Dyslipidemia	764 (74.0%)	488 (72.8%)	276 (77.5%)	0.475
Chronic renal failure	16 (1.6%)	9 (1.3%)	7 (2.0%)	0.440
Arterial hypertension	962 (93.2%)	632 (93.5%)	330 (92.7%)	0.928
Smoking	598 (57.9%)	402 (59.5%)	196 (55.1%)	0.479
History of AMI	632 (61.3%)	420 (62.1%)	212 (59.6%)	0.691
History of CABG	20 (1.9%)	12 (1.8%)	8 (2.2%)	0.608
History of PCI	281 (27.2%)	181 (26.8%)	100 (28.1%)	0.733
Cerebrovascular diseases	57 (5.5%)	34 (5.0%)	23 (6.5%)	0.366
Peripheral arterial diseases	43 (4.2%)	26 (3.8%)	17 (4.8%)	0.496
Left ventricular ejection fraction. %	59.89 ± 8.07	59.86 ± 7.72	59.94 ± 8.70	0.918
Indications for intervention:				
– silent myocardial	10 (1.0%)	5 (0.7%)	5 (1.4%)	0.305
– stable angina	1005 (97.4%)	657 (97.2%)	348 (97.8%)	0.951
– unstable angina	12 (1.2%)	10 (1.5%)	2 (0.6%)	0.196
– non-STEMI	2 (0.2%)	1 (0.1%)	1 (0.3%)	0.645
– STEMI	2 (0.2%)	1 (0.1%)	1 (0.3%)	0.645

The verification of the conformity of the distribution of values for the analyzed parameter to the normal distribution law was conducted using Kolmogorov-Smirnov test with Lilliefors modification. As already the first stage of statistical analysis showed, that the distribution of the values of most analyzed samples is not conform to the normal distribution law, their comparison and the evaluation of the found differences were done using non-parametric criteria: for independent samples – Mann–Whitney U-test; for the verification of differences between two paired samples – Wilcoxon T-test. $p \leqslant 0.05$ was considered statistically significant. The correlation ratio was evaluated using Spearman's rank correlation coefficient.

Mean characteristics of the samples in the tables are presented as an arithmetical mean for the sampled population ± standard deviation (SD).

Results

From the total number of 1032 patients, 676 were operated under IVUS guidance, and 356 – under quantitative angiographic guidance. The comparison of patients' characteristics (Table 1) did not reveal significant differences between the subgroups of quantitative angiography and IVUS for any of the indices. Meanwhile, the analysis of procedure-related parameters (Table 2) showed the differences between certain parameters. In view of the attitudes adopted in our hospital, the interventions on the left main coronary artery can be performed only under IVUS guidance; so, in case of this pathology the patients could be transferred from the angiography subgroup to the IVUS subgroup at the operator's choice. Hence, the number of patients with the disease of the left main coronary artery and bifurcation lesions was significantly higher in the IVUS subgroup; thus, the patients from this subgroup in general had more severe disease. Higher number of stents per lesion, larger diameter of the first stent , higher total length of the stents used, as well as higher maximal diameter of the balloon used for postdilatation in the IVUS subgroup can be explained by the particularities of procedural technology.

In total, as one can see from the Table 2, the trial involved the patients with rather complex morphology, which is confirmed by the number of patients with multivessel disease (56%), the incidence of B2 or C type lesions (98.8%), bifurcation stenoses (12.4%), chronic occlusions (11.4%), the lesion's length over 20 mm (84.9%), as well as by the average total length of the stented segment > 39 mm.

Angiographic indices (Table 3) were analyzed before and after the procedure, as well as after predilatation. The last subgroup was assigned in view of the necessity of comparison

Table 2. Procedure-related parameters

Parameter	Total (n = 1032)	IVUS subgroupa (n = 676)	Angiography subgroupa (n = 356)	p_{3-4}
1	2	3	4	5
Target artery:				
LAD	500 (48.4%)	339 (50.1%)	161 (45.2%)	0.373
CxA	241 (23.4%)	148 (21.9%)	93 (25.8%)	0.231
IB	18 (1.7%)	12 (1.8%)	6 (1.7%)	0.918
RCA	268 (26.0%)	173 (25.6%)	95 (26.7%)	0.771
Left main CA	38 (3.7%)	35 (5.2%)	3 (0.8%)	<0.001
Multivessel disease	578 (56.0%)	368 (54.4%)	210 (59.0%)	0.459
B2 or C lesion type	1020 (98.8%)	667 (98.7%)	353 (99.2%)	0.958
Bifurcation lesion	128 (12.4%)	96 (14.2%)	32 (9.0%)	0.032
Thrombus-containing lesions	4 (0.4%)	2 (0.3%)	2 (0.6%)	0.515
Calcification	121 (11.7%)	84 (12.4%)	37 (10.4%)	0.390
Occlusion	118 (11.4%)	80 (11.8%)	38 (10.7%)	0.619
Stents per lesion	1.47 ± 0.50	1.51 ± 0.50	1.38 ± 0.49	<0.001
Diameter of the 1st stent. mm	3.47 ± 0.42	3.49 ± 0.42	3.43 ± 0.41	0.024
Length of the 1st stent. mm	26.08 ± 6.95	25.98 ± 6.89	26.26 ± 7.09	0.542
Diameter of the 2nd stent. mm	3.09 ± 0.38	3.09 ± 0.39	3.10 ± 0.36	0.793
Length of the 2nd stent. mm	26.90 ± 6.77	26.93 ± 6.94	26.91 ± 6.36	0.982
Total length of stents per lesion. mm	38.61 ± 15.71	39.69 ± 15.98	36.68 ± 15.13	0.003
Maximal balloon diameter. mm	3.70 ± 0.50	3.79 ± 0.51	3.56 ± 0.44	<0.001
Maximal inflation pressure. mm Hg	13.97 ± 2.50	13.97 ± 2.53	13.91 ± 2.48	0.750
Additional balloon on the base of IVUS data	133 (12.9%)	133 (19.7%)	–	–
Use of IIb/IIIa inhibitors	7 (0.7%)	4 (0.6%)	3 (0.8%)	0.643

Table 3. Angiographic data

Parameter	Total (n = 1032)	IVUS subgroup (n = 676)	Angiography subgroup (n = 356)	p_{2-3}	p_{2-4}	p_{3-4}
1	2	3	4	5	6	7
Before the procedure						
Minimal lumen diameter, mm	1.12 ± 0.62	1.14 ± 0.62	1.10 ± 0.61	0.51	0.38	0.18
Reference vessel diameter, mm	2.96 ± 0.60	2.96 ± 0.61	2.96 ± 0.57	0.95	0.98	0.98
Lesion's length, mm	35.32 ± 14.83	36.15 ± 14.93	33.91 ± 14.47	0.25	0.12	0.02
Lesion's length ⩾ 20 mm	875 (84.87%)	577 (85.35%)	299 (83.99%)	0.92	0.92	0.87
Lumen area, mm^2	1.30 ± 1.07	1.33 ± 1.08	1.24 ± 1.04	0.54	0.39	0.21
Lumen volume in the segment, mm^3	170.68 ± 104.21	176.60 ± 106.63	160.95 ± 98.34	0.28	0.17	0.03
Plaque volume in the segment, mm^3	83.04 ± 64.15	84.09 ± 66.93	81.47 ± 58.83	0.89	0.92	0.84
Stenosis diameter, %	62.18 ± 19.40	61.66 ± 19.48	63.38 ± 19.17	0.43	0.26	0.10
Stenosis area, %	81.98 ± 12.71	81.46 ± 12.87	82.88 ± 12.33	0.42	0.25	0.09
After predilatation						
Minimal lumen diameter, mm	1.38 ± 0.40	1.42 ± 0.39	1.32 ± 0.42	0.06	0.006	<0.001
Reference vessel diameter, mm	2.96 ± 0.59	2.96 ± 0.60	2.96 ± 0.58	0.94	0.87	0.83
Lumen area, mm^2	1.64 ± 0.94	1.72 ± 0.93	1.52 ± 1.01	0.05	0.007	<0.001
Lumen volume in the segment, mm^3	173.76 ± 102.25	179.44 ± 104.63	164.08 ± 96.74	0.25	0.13	0.023
Plaque volume in the segment, mm^3	86.12 ± 67.51	87.32 ± 70.65	84.27 ± 61.46	0.96	0.99	0.97
Stenosis diameter, %	52.83 ± 12.11	51.63 ± 11.57	54.98 ± 12.84	0.06	0.007	<0.001
Stenosis area, %	76.27 ± 11.49	75.23 ± 11.28	78.07 ± 11.71	0.05	0.006	<0.001
After the procedure						
Minimal lumen diameter, mm	2.87 ± 0.46	2.88 ± 0.47	2.83 ± 0.45	0.58	0.39	0.22
Reference vessel diameter, mm	3.16 ± 0.51	3.16 ± 0.53	3.15 ± 0.48	0.88	0.81	0.73
Lumen area, mm^2	6.60 ± 2.12	6.72 ± 2.24	6.43 ± 1.98	0.58	0.40	0.22
Lumen volume in the segment, mm^3	308.66 ± 163.00	322.75 ± 169.05	233.75 ± 172.54	0.11	0.027	0.001
Plaque volume in the segment, mm^3	34.11 ± 44.72	36.21 ± 45.83	29.04 ± 40.55	0.37	0.18	0.05
Stenosis diameter, %	9.20 ± 5.84	8.69 ± 5.84	10.17 ± 5.72	0.07	0.005	<0.001
Stenosis area, %	17.22 ± 10.36	16.33 ± 10.44	18.92 ± 9.99	0.07	0.006	<0.001

Table 4. IVUS data

Indices	Baseline lesion			Control study		p_{3-5}	p_{3-6}	p_{5-6}
	Proximal reference segment	Maximal stenosis	Distal reference segment	Site of maximal baseline stenosis	Minimal stent diameter			
1	2	3	4	5	6	7	8	9
Minimal diameter, mm	3.37 ± 0.63	1.92 ± 0.30	2.87 ± 0.59	3.10 ± 0.49	2.79 ± 0.49	<0.001	<0.001	<0.001
Minimal vessel diameter, mm	4.53 ± 0.73	4.11 ± 0.75	3.56 ± 0.87	4.54 ± 0.68	3.96 ± 0.79	<0.001	<0.001	<0.001
Lumen area, mm^2	10.77 ± 3.90	3.63 ± 1.21	7.64 ± 0.25	9.08 ± 2.58	7.40 ± 2.52	<0.001	<0.001	<0.001
Vessel area, mm^2	18.15 ± 5.67	14.67 ± 4.51	11.17 ± 4.98	18.21 ± 5.27	14.03 ± 5.64	<0.001	<0.001	<0.001
Plaque area, mm^2	7.41 ± 3.49	11.55 ± 4.96	3.60 ± 2.53	9.13 ± 3.48	6.62 ± 3.76	<0.001	<0.001	<0.001
Stenosis diameter, %	25.28 ± 9.64	52.63 ± 8.12	18.25 ± 7.76	31.42 ± 7.07	28.50 ± 9.34	<0.001	<0.001	<0.001
Stenosis area, %	40.11 ± 12.70	74.63 ± 7.49	30.36 ± 10.53	49.20 ± 8.43	44.67 ± 11.45	<0.001	<0.001	<0.001
Eccentricity index	0.83 ± 0.24	0.83 ± 0.10	0.84 ± 0.24	0.86 ± 0.07	0.84 ± 0.01	<0.001	0.391	0.005
Plaque eccentricity index	0.34 ± 0.28	0.32 ± 0.37	0.42 ± 0.28	0.37 ± 0.18	0.37 ± 0.03	<0.001	<0.001	0.350

with the IVUS data (in cases of occlusion or critical stenosis the advancement of the transducer and the realization of IVUS were feasible only after predilatation).

Before the procedure, angiographic indices did not differ in the subgroups of IVUS and angiography, at the exception of higher lesion's length and the volume of the lumen in the segment in patients operated under IVUS guidance. Higher values of the minimal diameter, the area and the volume of the lumen, and, respectively, lower stenosis degree as judged by the area and the diameter were obtained after predilatation in the subgroup of IVUS. After the procedure, higher volume of the lumen and lower stenosis degree as judged by the diameter and the area were seen in the group of IVUS.

Intravascular ultrasonic scanning after randomization was performed in 2/3 of the patients involved in the trial – 676. As stated previously, while analyzing the angiographic data, the baseline study (Table 4), in fact, corresponds to the study after predilatation. The comparison of quantitative indices in the area of maximal stenosis in the proximal, as well as in the distal reference segments, revealed their obligate significant differences. Herewith, there were reliable differences between the studied indices in the reference segments, which is primarily related to the significant length of the lesion. Control intravascular ultrasound examination showed, that the maximal residual stenosis almost always did not correspond to the site of initial maximal stenosis, and all quantitative indices for these two segments were significantly different. Most commonly, the maximal postoperative stenosis was located closer to the distal part of the lesion, and smaller diameter and area of the lumen in this segment could be partly explained by smaller size of the vessel itself. This is confirmed by the fact, that the area and the diameter of the stenosis in the site of minimal residual lumen were smaller, than in the site of initial maximal stenosis.

Of special interest is direct comparison between quantitative indices calculated with the help of angiography and IVUS at the initial stage of the procedure in 676 patients from the subgroup of IVUS (Table 5). The data suggest, that the absolute values of the measured parameters significantly differed, herewith the estimated, relative values of stenosis diameter and area are quite close. We noted a moderate positive correlation between the measured angiographic and ultrasonic parameters and a weak one – between the relative parameters.

Table 5. Comparison of angiography and IVUS data before stenting (after predilatation)

Parameter	Angiography	IVUS	p	r
1	2	3	4	5
Minimal lumen diameter, mm	1.42 ± 0.39	1.92 ± 0.30	0.001	0.35**
Reference vessel diameter, mm	2.96 ± 0.60	4.11 ± 0.75	0.001	0.42**
Lumen area, mm^2	1.72 ± 0.93	3.63 ± 1.21	0.001	0.34**
Vessel area, mm^2	7.15 ± 2.85	14.67 ± 4.51	0.001	0.43**
Stenosis diameter, %	51.63 ± 11.57	52.63 ± 8.12	0.012	0.25**
Stenosis area, %	75.23 ± 11.28	74.63 ± 7.49	0.15	0.28**

Here, and in Table 8: * – significant correlation at 0.05 (two-tailed). ** – significant correlation at 0.01 (two-tailed)..

Thus, angiographic data can be quite sufficient for the evaluation of the degree and the significance of the stenosis, while providing rather rough landmarks for the selection of necessary instruments for the intervention.

The data of control optical coherence tomography performed in almost all patients (1020 – 98.8%), were analyzed within the subgroups similar to the quantitative angiography (the subgroups of angiography, IVUS and all patients). Qualitative and quantitative analyses were applied to the same segments as during intravascular ultrasonic examination – the sites of minimal stent diameter, maximal baseline stenosis, as well as proximal and distal stent segments (Table 6).

In all the subgroups analyzed, at the site of minimal stent diameter all parameters significantly differed from those in three other segments, at the exception of lumen area in comparison with the distal stent segment. In common with IVUS data, the site of minimal stent diameter usually did not correspond to the maximal baseline stenosis.

The comparison of postoperative data of angiography and optical coherence tomography in the subgroup of angiography and in the whole group of patients (Table 7) revealed significant differences in all the parameters, moreover, these differences were of divergent character: according to OCT data, the absolute values of the minimal lumen diameter were smaller, and those of all the remaining indices – bigger. There was a moderate positive correlation between the measured indices obtained with angiography and OCT and a weak positive correlation – between the relative values.

In the group of IVUS, it was possible to compare postoperative data obtained with the help of all three methods – angiography, IVUS and OCT (Table 8). Significant differences were noted while comparing IVUS and OCT data for all the pairs, at the exception of minimal lumen diameter and the index of plaque eccentricity. Herewith, the absolute values of minimal lumen diameter were rather close and the maximal values were obtained by angiography; for all the remaining parameters, the minimal values were obtained with angiography and the maximal ones – with IVUS (except for lumen area, which was bigger when measured by OCT than by IVUS). As in previously mentioned comparisons, there was a moderate positive correlation between the measured parameters in all pairs of the comparison and a weak positive correlation between the relative values.

Immediate effect of the intervention was obtained in all 1032 patients. Besides, 5 patients in whom final OCT control has revealed a pathology requiring the changes in the procedural protocol were excluded from the study. In 3 cases OCT revealed a large volume of atheromatous masses prolapse with thrombi depositions, which necessitated the implantation of additional stents. In another two cases, OCT revealed diastasis between the stents, which also required additional stenting in view of intimal dissection in this area.

One patient from the subgroup of angiography died in early postoperative (within 1 day after the procedure) because of myocardial infarction in the territory of a non-operated artery with baseline angiographically insignificant lesion. There were no other in-hospital significant cardiovascular events. Two cases of hemopericardium in patients after recanalization of chronic occlusions had no clinical consequences – in one case the signs stopped after pericardial drainage, in another case only the follow-up was necessary. No other complications were noted.

Within 1 month after the intervention 955 patients (92.5%) underwent out-patient examination in the regional polyclinic. There were neither cardiovascular events, nor objective signs of the aggravation of patients' condition. Subjective improvement in comparison with preoperative condition was noted in 820 patients (85.9%), 124 patients (13.0%) stated no changes in their condition, 11 (1.2%) com-

Table 6. OCT data

Parameter	Control				p_{2-3}	p_{2-4}	p_{2-5}
	Minimal stent diameter	Maximal baseline stenosis	Proximal stent segment	Distal stent segment			
1	2	3	4	5	6	7	8
All patients							
Minimal lumen diameter, mm	2.77 ± 0.54	2.93 ± 0.53	3.36 ± 0.53	2.84 ± 0.53	<0.001	<0.001	<0.001
Minimal vessel diameter, mm	3.74 ± 0.64	3.89 ± 0.64	4.33 ± 1.56	3.53 ± 0.69	<0.001	<0.001	<0.001
Lumen area, mm^2	7.46 ± 2.57	8.26 ± 2.69	10.22 ± 3.40	7.18 ± 2.77	<0.001	<0.001	0.063
Vessel area, mm^2	11.93 ± 13.20	13.26 ± 4.13	15.85 ± 4.70	10.75 ± 4.14	<0.001	<0.001	<0.001
Plaque area, mm^2	4.81± 2.15	5.09 ± 2.12	5.96 ± 2.33	3.73 ± 2.11	<0.001	<0.001	<0.001
Stenosis diameter, %	26.46 ± 7.31	24.72 ± 6.96	21.81 ± 6.65	19.24 ± 6.68	<0.001	<0.001	<0.001
Stenosis area,%	38.88 ± 8.31	37.89 ± 8.14	35.60 ± 8.39	32.51 ± 9.32	<0.001	<0.001	<0.001
Eccentricity index of the lumen	0.84 ± 0.10	0.87 ± 1.02	–	–	<0.001	–	–
Eccentricity index of the plaque	0.40 ± 0.32	0.40 ± 0.17	–	–	0.102	–	–
IVUS subgroup							
Minimal lumen diameter, mm	2.80 ± 0.54	2.99 ± 0.53	3.41 ± 0.55	2.84 ± 0.53	<0.001	<0.001	<0.001
Minimal vessel diameter, mm	3.78 ± 0.65	3.95 ± 0.65	4.40 ± 1.86	3.52 ± 0.67	<0.001	<0.001	<0.001
Lumen area, mm^2	7.77 ± 2.76	8.59 ± 2.74	10.57 ± 3.59	7.17 ± 2.83	<0.001	<0.001	0.246
Vessel area, mm^2	12.05 ± 4.04	13.68 ± 4.21	16.26 ± 4.93	10.70 ± 4.07	<0.001	<0.001	<0.001
Plaque area, mm^2	4.82 ± 2.14	5.22 ± 2.15	5.97 ± 2.37	3.69 ± 2.09	<0.001	<0.001	<0.001
Stenosis diameter, %	26.55 ± 7.42	24.96 ± 7.04	21.66 ± 6.72	19.06 ± 6.62	<0.001	<0.001	<0.001
Stenosis area,%	38.81 ± 8.06	37.74 ± 7.99	35.02 ± 8.17	32.45 ± 9.43	<0.001	<0.001	<0.001
Eccentricity index of the lumen	0.84 ± 0.10	0.84 ± 0.09	–	–	<0.001	–	–
Eccentricity index of the plaque	0.40 ± 0.34	0.41 ± 0.18	–	–	0.003	–	–
Angiography subgroup							
Minimal lumen diameter, mm	2.71 ± 0.52	2.81 ± 0.51	3.28 ± 0.52	2.84 ± 0.54	<0.001	<0.001	<0.001
Minimal vessel diameter, mm	3.66 ± 0.63	3.77 ± 0.63	4.23 ± 0.75	3.56 ± 0.81	<0.001	<0.001	0.005
Lumen area, mm^2	7.07 ± 2.45	7.60 ± 2.50	9.64 ± 3.11	7.16 ± 2.72	<0.001	<0.001	0.176
Vessel area, mm^2	11.57 ± 3.64	12.38 ± 3.84	15.07 ± 4.38	10.75 ± 4.21	<0.001	<0.001	<0.001
Plaque area, mm^2	4.63 ± 1.99	4.82 ± 1.95	5.94 ± 2.23	3.72 ± 2.07	0.099	<0.001	<0.001
Stenosis diameter, %	26.30 ± 7.12	25.27 ± 6.64	22.56 ± 6.74	19.21 ± 6.72	<0.001	<0.001	<0.001
Stenosis area, %	39.02 ± 8.77	38.00 ± 8.68	36.55 ± 8.71	32.51 ± 9.14	0.003	<0.001	<0.001
Eccentricity index of the lumen	0.81 ± 0.11	0.92 ± 1.38	–	–	<0.001	–	–
Eccentricity index of the plaque	0.40 ± 0.18	0.41 ± 0.17	–	–	0.503	–	–

Table 7. Comparison of postoperative angiographic and OCT data in all patients and in the subgroup of angiography

Parameter	All patients				Singroup of angiography			
	Angiography	OCT	p_{2-3}	r_{2-3}	Angiography	OCT	p_{6-7}	r_{6-7}
1	2	3	4	5	6	7	8	9
Minimal lumen diameter, mm	2.87 ± 0.46	2.77 ± 0.54	0.001	0.61**	2.83 ± 0.45	2.71 ± 0.52	0.001	0.61**
Reference vessel diameter, mm	3.16 ± 0.51	3.74 ± 0.64	0.001	0.50**	3.15 ± 0.48	3.66 ± 0.63	0.001	0.51**
Lumen area, mm^2	6.60 ± 2.12	7.46 ± 2.57	0.001	0.61**	6.43 ± 1.98	7.07 ± 2.45	0.001	0.61**
Vessel area, mm^2	7.98 ± 2.52	11.93 ± 3.63	0.001	0.50**	7.94 ± 2.37	11.57 ± 3.64	0.001	0.49**
Stenosis diameter, %	9.20 ± 5.84	26.46 ± 7.31	0.001	0.17**	10.17 ± 5.72	26.30 ± 7.12	0.001	0.25**
Stenosis area, %	17.22 ± 10.36	38.88 ± 8.31	0.001	0.07**	18.92 ± 9.99	39.02 ± 8.77	0.001	0.12*

Table 8. Comparison of postoperative data of angiography, IVUS and OCT in the subgroup of IVUS

Parameter	Подгруппа ВСУЗИ								
	Angiography	IVUS	OCT	p_{2-3}	p_{2-4}	p_{3-4}	r_{2-3}	r_{2-4}	r_{3-4}
1	2	3	4	5	6	7	8	9	10
Minimal lumen diameter, mm	2.88 ± 0.47	2.79 ± 0.49	2.80 ± 0.54	0.001	0.001	0.87	0.58**	0.62**	0.57**
Reference vessel diameter, mm	3.16 ± 0.53	3.96 ± 0.79	3.78 ± 0.65	0.001	0.001	0.001	0.51**	0.51**	0.47**
Lumen area, mm^2	6.72 ± 2.24	7.40 ± 2.52	7.77 ± 2.76	0.001	0.001	0.004	0.59**	0.62**	0.58**
Stenosis diameter, %	8.69 ± 5.84	28.50 ± 9.34	26.55 ± 7.42	0.001	0.001	0.001	0.10*	0.12**	0.19**
Stenosis area, %	16.33 ± 10.44	44.67 ± 11.45	38.81 ± 8.06	0.001	0.001	0.001	0.06	0.06	0.13**
Eccentricity index of the lumen	–	0.84 ± 0.01	0.82 ± 0.10	–	0.001	0.001	–	–	0.30**
Eccentricity index of the plaque	–	0.37 ± 0.03	0.38 ± 0.17	–	0.001	0.19	–	–	0.20**

plained of subjective aggravation. EchoCG revealed increased ejection fraction and/or decreased hypokinetic area in 72.2% of patients, in 18.4% – the EchoCG indices were not significantly changed, in 9.4% – the ejection fraction decreased. There were no cases of heart-related readmission, no repeated coronary angiography was needed.

Discussion

Immediate and early (one month) results of the treatment of patients included in the randomized "ORENBURG" trial, suggest good clinical effect, with a very low percentage of major cardiovascular events – 0.1% (0% in the subgroup of IVUS, 0.28% in the subgroup of angiography). Herewith, as stated above, the trial comprised the patients with rather complex morphology, many patients had multivessel disease, bifurcation stenoses, chronic occlusions. The overwhelming majority of patients had B2 or C type of lesion with the length of the diseased segment over 20 mm and the average length of the stented segment was over 39 mm.

Obviously, the early results of percutaneous intervention are primarily influenced by the right choice of instruments based on an adequate evaluation of the vessel's size. In this connection, one has to note two factors contributing to favorable results in our patients. Firstly, prior to elective procedures all patients undergo mandatory quantitative angiography, and its version used in our hospital (CAAS 5) allows to obtain high-quality estimation. Secondly, the majority of our operators possess a big experience with intravascular ultrasound and, so, have "ultrasound-trained eyes" (12), and make an appropriate upward adjustment while selecting the instruments on the base of angiographic data analysis.

The patients from the subgroup operated under IVUS control had bigger length of the lesion and volume of the segment's lumen, and after the intervention they had bigger volume of the lumen, smaller diameter and area of the stenosis, in comparison with the subgroup of angiographic guidance. Besides, in the subgroup of IVUS there were more stents used per lesion, as well as higher diameters of the first stent, higher total length of the stents and higher maximal diameter of the balloon used for postdilatation. These data coincide with the results of most studies comparing the strategies of stenting under angiographic or IVUS guidance. In particular, in the IVUS-XPL trial, the use of IVUS guidance was associated with significantly higher frequency of postdilatation, bigger size of the final balloon, higher maximal inflation pressure and bigger vessel's diameter after stenting.

The absolute values of the measured indices obtained with IVUS, in our study were significantly higher than the angiographic results, while the relative values – stenosis diameter and area – were quite close.

The design of our study involved additional in-stent manipulations in cases, when the parameters of the optimal stenting were not obtained. Additional in-stent angioplasty after control IVUS was applied in 10.1% of patients. Additional impact allowed us to significantly improve all quantitative indices. However, the optimal results with the achievement of target parameters, as judged by IVUS < was obtained only in 71% of patients. Herewith, in one fourth of patients from the subgroup of IVUS (25.6%) who had optimal results as judged by IVUS data, control optical coherence tomography suggested suboptimal effect, and in 28.9% suboptimal results were revealed by both IVUS and OCT.

In the subgroup of angiographic guidance, OCT confirmed the optimal results in 47.6%, which is even somewhat higher than in the subgroup of IVUS (45.4%). This is related to the fact, that the criteria of implantation optimality with IVUS guidance are directed mainly at the achievement of adequate parameters of stent deployment, while OCT with its 10-fold higher resolution, fixes primarily intraluminal problems connected with the dissections, tissue prolapse, malapposition and thrombi (thus, allowing for less exact evaluation of quantitative parameters). One cannot exclude, that the additional manipulations, aimed at optimization of IVUS data, can provoke the manifestations which can be judged as suboptimal when evaluated by OCT – tissue dissection and prolapse – however, clinical significance of such changes has to be studied.

Direct comparison of the results of all three methods of study – quantitative angiography, intravascular ultrasound and optical coherence tomography – was feasible after the intervention in patients from the subgroup of IVUS guidance. Herewith, statistically significant lesions were noted by comparison of practically all pairs of indices, with moderate positive correlation. For all the indices, at the exception of minimal lumen diameter (which was similar with all three methods), the absolute values of the measured parameters increased in raw "angiograpgy – OCT – IVUS".

Conclusion

Immediate and early (one month) results of the single-centered randomized controlled prospective trial "ORENBURG" suggest good clinical effect, with very low incidence of major cardiovascular events – one cardiac death, not related to the target territory, in the absence of other complications. This trial comprising 1032 patients is the second largest randomized trial comparing the strategies of stenting under the guidance of quantitative angiography or intravascular ultrasound. Despite a rather "aggressive" strategy of stenting, with additional intervention after IVUS control if necessary, the number of suboptimal results revealed by optical coherence tomography, was comparable in the subgroups of angiography and IVUS. In cases, when direct comparison of angiography, IVUS and OCT was feasible, in most cases the methods demonstrated significant differences of the measured parameters, with close relative values.

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