GENERAL REVIEW

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Structural features of arterial grafts important for surgical myocardial revascularization: Part II – Histology of the radial, inferior epigastric, and right gastroepiploic arteries

Strukturne karakteristike arterijskih graftova važnih za hiruršku revaskularizaciju miokarda: Deo II – Histologija radijalne, donje epigastrične i desne gastroepipliočne arterije

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Introduction

Clinical experience and numerous research indicate that arterial grafts are superior to venous grafts for surgical revascularization of myocardium. Arterial grafts in comparison to vein grafts of the great saphenous vein have higher patency rate in early and late postoperative period. After complete arterial revascularization, the in-hospital mortality is between 0.5% and 2.2%, with the survival rate of 99% and the major adverse events-free survival in 89% of patients after 12 months [1, 2]. In the period of 1 to 3 years postoperatively, the patency rate of the used arterial grafts is between 96.5% and 98.3% [1].

Besides the left and the right internal thoracic arteries, radial, inferior epigastric and the right gastroepiploic arteries are used for complete arterial revascularization and treatment of multivessel disease. The complex T- and Y- forms of composite grafts, the need for continual improvement of the surgical technique and harvesting procedure initiated studies focused on biological determinants of arterial grafts, their structure and functional remodeling. The final goal of morphological and morphometric analyses is to find the optimal combination of grafts ideally matched for the needs of patients.

Histology of the radial artery

The radial artery (RA) represents a classically structured muscular type artery (Figures 1A–C). The *tunica intima* of this artery is typically organized and made up of endothelium and subendothelial connective tissue. In experimental conditions, the RA is proved to have efficient supply of nitric oxide. Studies that analyzed the endothelium dependent vasodilatation induced by nitric oxide in the RA in comparison to the internal thoracic artery (ITA) brought opposite results. One group of results confirm a significantly reduced NO level in the RA [3], while the other group show that both endothelium-dependent and endothelium-independent vasodilatation are preserved and not different from the ITA [4]. The means of the intima thickness of the RA

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varies between 45.7 μm and 60.4 μm and steadily and significantly increases with aging [5].

The RA has the most prominent arteriosclerosis among arterial grafts, including both atherosclerosis and Mönckeberg medial calcific sclerosis [5]. Preoperative assessment of atherosclerosis of native arteries is an important parameter, since it determines the outcome of surgical revascularization and complications including recurrent *angina pectoris* and myocardial infarction [4, 6]. Graft patency is compromised by the progression of native atherosclerosis of the arterial graft.

Comparative analysis of the presence of atherosclerosis in different arterial grafts in general population indicated that only 7.09% of the RA segments were without changes and the rest (92.91%) had diffuse or focal intimal hyperplasia. Among the later, 24% were with Mönckeberg medial calcific sclerosis [5]. Ruengsakulrach et al. [7], in their vast series, described 94% of the RA with intimal hyperplasia along with 13.3% of arteries with medial calcific sclerosis. In their study, only 5% of arteries had atherosclerosis. Risk factors associated with intimal hyperplasia and atherosclerosis of the RA are aging, smoking, peripheral vascular disease and *diabetes mellitus*.

In a study that analyzed final 15% of the arterial length, 28% of arteries had stenosis of the lumen greater than 50% [8]. As shown with other studies 1–7% of the radial arteries were not suitable for the coronary artery by-pass grafting (CABG) procedure [9, 10]. However, early and mid-term graft patency rate were not affected by this relatively higher level of native atherosclerosis as compared to the ITA [11, 12]. The thickness of the intima did not increase even 37.6 ± 7.2 months after the surgery [12]. The long-term patency rate of the RA after 105 ± 9 months was 91.6% [4].

The internal elastic membrane is well-developed throughout the length of the radial artery. It contains almost twice the number of discontinuities (8.6/mm) than the same structure in the ITA (4.5/mm) [13]. The size of these fenestrations is also almost twice the size of fenestrations of the ITA in the same age group (2.73 ± 0.24 μm *vs* 4.27 ± 0.78 μm in forties and 2.72 ± 0.72 μm *vs* 4.10 ± 0.35 μm in sixties) [5]. The universal rule observed for the elastic lamellae of all arterial grafts is that their integrity diminishes with aging making the arteries prone to vascular smooth muscle cells migration and intimal hyperplasia development [14–16].

Tunica media of the RA is composed of circularly distributed smooth muscle cells, which is why this artery is prone to spasm, especially when it is implanted in the conditions of high pressure and flow, like the position of aorto-coronary by-pass conduit. The RA has the thickest media of all described arterial grafts with a mean value of 352.6 ± 10.2 μm, and variations of mean values between 302.4 μm and 450.8 μm [5]. The thickness of the media increases significantly with aging [5]. High resolution echo-tracking with Doppler and A-mode detection of the vascular structure confirmed hypertrophy of the RA media and hyperplasia of the intima associated with luminal narrowing in patients with coronary artery disease, candidates for the CABG surgery [17]. Despite that, the intima/media thickness was not increased, not even 3 to 4 years after implantation of the RA as CABG graft, as determined with similar, ultrasound studies [12].

The vasospasm that follows CABG surgery with the RA is surpassed with the usage of calcium channel blockers and papaverin-NaCl solutions. Nevertheless, the research studies have shown that papaverin-NaCl solution significantly damages endothelial layer of the RA [18].

This artery is characterized by the thickest wall among the applicable arterial grafts (about 550 μm). The outer layer (*tunica adventitia*) contains well-developed blood vessels (*vasa vasorum*), which have a significant stake in the perfusion of the artery wall, including its middle layer (*tunica media*) [5].

The radial artery is characterized by the presence of radially oriented fibers of type I collagen, which penetrate from the adventitial layer to the media [5] (Figures 1A and B). This finding suggests that a very developed and meticulous surgical technique is needed for the preparation of this artery, and that any damage of the wall during the preparation may affect the stability of the media and compromise the long-term graft patency. In support of this finding is a well-known fact in the literature, that intimal hyperplasia can be avoided with the preparation of the RA together with the surrounding periadventitial tissue and accompanying veins [8].

Gender specific differences. The radial arteries of females have significantly smaller lumen and perimeter, but there is no significant difference in the thickness of the intima and the media [19] among genders. Our results show no significant difference in the basic morphometric parameters of the males and females [5].

Left-to right specific differences. No significant difference in the basic morphometric parameters of left and right arteries were described [5].

Use in surgical myocardial revascularization

The RA was firstly used as an arterial graft in 1973 [20]. Shortly after that, the use of this artery was abandoned due to its strong tendency of spasm. However, during the last years of the twentieth century, thanks to the introduction of calcium channel blockers in the postoperative period, the use of this arterial graft was re-actualized [21, 22]. The patency rate with this new approach was 93.5% in the period of 9.2 months, i.e. 90–93% during the postoperative period of 1.5 ± 1.1 years [8, 9, 21]. This graft can be used in patients with impaired left ventricular function [23] and even after 10 years of CABG, the patency of the RA grafts goes up to 83% [24].

The RA got its special significance thanks to new surgical techniques of composite grafts, modern methods of ultrasound dissection and application of endoscopic dissection of the RA, which gives better cosmetic results, does not impair graft patency and postoperative outcome and gives rare neurological complications [25–27]. This artery has shown to be particularly suited for sequential anastomosis, as a part of composite grafts with good perioperative results, because of its bigger diameter compared to other arterial grafts [1, 28]. Comparison of the RA used as direct aorto-coronary conduit or as a part of T composite graft indicated that the outcome of the procedure depends primarily on the target vessel and its level of atherosclerosis and stenosis and not as much on the grafting strategy. Significantly worse prognosis was for the right coronary artery

as target vessel and vessels with stenosis ≤ 70% [29]. This conclusion potentiates again the fact, well-known for researchers in the arterial grafting domain, that the level of native atherosclerosis of coronary arteries, i.e. target vessels is important for the prediction of the CABG outcome [4, 30–32].

Good short-term postoperative results were reported when the RA was used with the left ITA for complete arterial revascularization of emergency patients with unstable angina and/or critical coronary stenosis with high risk for acute myocardial infarction [33]. This is also proved to be a safe procedure for elderly patients, older than 70 years [34].

However, the routine usage of the RA graft is still an issue for debate, in the search for the ideal second graft and a perfect match for the ITA [35]. There are supporters of revascularization with the ITA and saphenous vein (SV) graft and studies that suggest superior outcome of the ITA/SV grafting to the ITA/RA grafting [6]. Perioperative outcomes are similar in these two groups, but long-term outcomes in the period of 0–6 years showed that overall mortality was greater in the ITA/SV group. Incidence of repeated catheterization and the need for revascularization were similar for the two groups [36]. However, in this study, Zacharias et al. [36] did not confirm a significantly better patency rate of ITA/RA grafts in comparision to ITA/SV grafts. As confirmed angiographically, in the period of 1.8 ± 1.4 years postoperatively, 77 out of 242 (31.8%) RA grafts were occluded, while 216 out of 588 (36.7%) SV grafts were occluded. The observed difference was not statistically significant ($p = 0.11$). Zacharias et al. [36], insisted upon significant difference ($p = 0.039$) in patency rate between RA grafts (70.07%) and SV grafts (59%) in patients that received both conduits. However, these conclusions were obtained in a non-randomized study, where RA and SV grafts by-passed coronary arteries with diverse rates of stenoses and different irrigation areas of myocardium, i.e. with different run-off areas. If the SV or the RA grafts were used in randomized conditions as conduits for the second largest target artery, the patency was not significantly different. It was 90% for the SV graft after 5 years and 80% after 9 years [37].

Meta-analysis and systematic review of 35 studies using a random-effect model and odds ratio for statistical elaboration proved that mid-term (1–5 years) and long-term (> 5 years) patency was better in the RA grafts in comparision to SV grafts [38].

The results of RAPS (Radial Artery Patency Study) confirmed that graft occlusion was lower in RA than in SV grafts at the mean period of 7.7 ± 1.5 years after surgery [39]. There were 12% of functionally occluded RA grafts and 19.7% functionally occluded SV grafts, defining functional occlusion as lack of thrombolysis in myocardial infarction flow grade 3. There were 8.9% of completely occluded RA grafts and 18.6% completely occluded SV grafts [39]. In both cases, differences are proved to be statistically significant ($p = 0.03$ and $p = 0.002$, respectively) [39].

Histology of the inferior epigastric artery

The inferior epigastric artery is a muscular type artery, with typical three-layered organization (Figure 1E-F). The *tunica intima* of this artery consists of endothelium and a very thin layer of subendothelial connective tissue. The thickness of the inner layer (*tunica intima*) of this artery is smaller than the thickness of the *tunica intima* of the ITA and of all other arterial grafts [5]. The mean intima thickness is 6.6 ± 4.4 μm and it does not change significantly with aging [5, 40].

The inferior epigastric artery is the artery with the lowest atherosclerosis level among the arterial grafts. In our study, 71.6% of the samples were completely unchanged, while the rest 28.4% were with low grade, focal intimal hyperplasia. Many studies confirmed the lack of atherosclerosis even in those patients with known risks for atherosclerosis [41–44].

The internal elastic membrane is well-developed and contains a small number of fenestrations (4/mm). According to some studies, it is less than the number of fenestrations of the ITA (4.62/mm) [44], while other data suggest that the average number of discontinuities of the internal elastic membrane of the inferior epigastric artery is approximately the same as the number of fenestrations in the elastic-muscular segments of the ITA [45]. According to our results the number of fenestrations is 3.99 ± 0.54 mm in the forties and 4.79 ± 1.45 mm after 61 years of age [5]. The size of fenestrations is similar to the RA fenestrations and equals 3.79 ± 0.67 μm in persons between the age of 40 and 60, and 3.53 ± 0.78 μm after 61 years [5]. Although much of the effort was invested in the morphometric studies of the inner elastic membrane parameters, they do not differ between the grafts proportionally to the intimal hyperplasia or atherosclerosis level. As for the number of elastic lamellae in the ITA, elastic skeleton alone is not of key importance to the delay of atherosclerosis or intimal hyperplasia, it is rather the complex interaction of vascular smooth muscle cells and the extracellular matrix that has this effect [14].

The structure of the *tunica media* corresponds to muscular type arteries with a predomination of smooth muscle cells and few formed elastic lamellas in the proximal part, immediately after the take off from the external iliac artery [45]. The media thickness is 164.4 μm ± 51.3 μm and it is not changed during aging.

The mean value of the artery wall thickness is 315.7 ± 75.2 μm and ideally corresponds to the wall thickness of the coronary arteries [5]. Because of the muscle phenotype of the medial layer, this artery has a strong tendency for spasm, so the late postoperative results are not satisfactory [45]. The presence of *vasa vasorum* is limited to the adventitial layer, so the perfusion of the media comes entirely from the lumen. Within this layer, the presence of longitudinally arranged contractile myocytes was observed. Although we defined this artery, at the beginning, as the muscular type artery, the presence of longitudinally arranged smooth muscle cells in the *tunica adventitia* gives this artery a character of a specialized type of artery [5, 40]. The presence of the smooth muscle cells in the adventitia could be important for physiological adaptability of this artery in a way similar to coronary arteries, which contain bundles of longitudinal smooth muscle fibers in the subendothelial tissue. The presence of these muscle cells enables adaptation of coronary arteries to changes of length and diameter during systole and diastole [14, 40, 46].

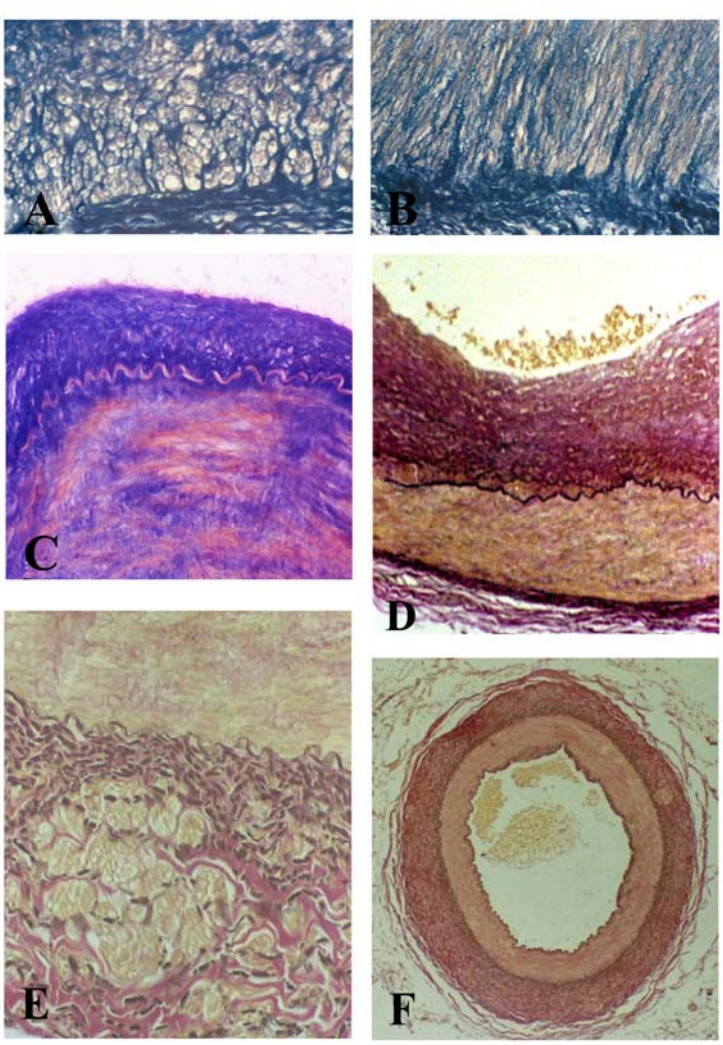

Fig. 1 – Arterial grafts – radial, inferior epigastric, right gastroepiploic arteries: A, B and C) the radial artery – Mallory staining for collagen fibers type I, [original magnification (A and B) ×64 and (C) ×100]; D) the right gastroepiploic artery – Weigert van Gieson staining for elastic fibers, [original magnification ×32]; E and F) the inferior epigastric artery – Weigert van Gieson staining for elastic fibers, [original magnification (E) ×256 and (F) ×8]. A and B – radial arrangement of collagen fibers in the media of the radial artery; C – the radial artery as the muscular type artery; D – the right gastroepiploic artery is the muscular type artery; intimal hyperplasia is present; E and F – the inferior epigastric artery is the muscular type artery; longitudinally arranged smooth muscle cells are present in the adventitia; there is no atherosclerosis.

In the adventitial layer of the inferior epigastric artery, numerous CD34 immunoreactive cells can be found. They are considered as highly active cells and a part of the pool of resident progenitor cells of the vascular wall. The presence of numerous CD34 immunoreactive endothelial cells was shown in the endothelium of the inferior epigastric artery as well, and in the ITA, whereas its expression in other analyzed grafts, as well as in the coronary arteries, is very scarce and reduced to rare, individual cells which are unevenly distributed along the circumference of a blood vessel [5].

If we look at the presence of CD34 positive endothelial cells as an indicator of blood vessel capacity for re-endothelization, there is a clear polarization, in terms of the distribution of this characteristic in the analyzed arterial grafts. The ITA and the inferior epigastric artery, which are characterized by the lowest degree of atherosclerosis, at the same time, have the biggest number of CD34 immunoreactive endothelial cells, as opposed to the coronary arteries, the radial artery and the right gastroepiploic arteries [5, 15].

Gender specific differences. The thickness of the media is higher in male patients [5].

Left-to right specific differences. Our results showed that left-sided arteries have thicker media than right-sided arteries in patients older than 61 year [5].

Use in surgical myocardial revascularization

The inferior epigastric artery was firstly used as free graft in 1988 [47]. Based on the results of preliminary studies, in the first two weeks after revascularization the graft patency rate was 97%, 12 months after the surgery the patency was 94%, and 14.8 months after the surgery the fatf patency was 79% [41, 48].

This artery is considered to be a suitable graft because of the extraperitoneal incision, avoidance of intra-abdominal dis-

section and the possibility of securing two grafts of sufficient length. Desirable characteristic of this graft is that the inferior epigastric artery *in situ*, represents an artery which rarely develops atherosclerosis. However, because of its position it represents a low pressure graft. The hypertensive stress to which it is exposed after implantation and anastomosis with the aorta, compromises the long-term patency of this graft [49].

Histology of the right gastroepiploic artery

The right gastroepiploic artery (GEA) is a typical muscular type artery (Figure 1D). The right GEA has a higher degree of intimal hyperplasia and atherosclerosis than the ITA or the inferior epigastric artery. Although the mean intima thickness is small (28.8 ± 33.1 μm), it grows dramatically after the age of 60 [5]. Studies show that 43% of the right gastroepiploic arteries have intimal hyperplasia with 25% of stenosis [50, 51]. In our series, 7.69% of sections had fibroatheroma, while 27.35% had no changes. The rest of 64.96% had intimal hyperplasia [5]. Among all analyzed grafts, the thickness of the intima is the lowest in the inferior epigastric artery, then comes the ITA and the right GEA, while the RA has the highest value of the intima thickness. These differences are statistically significant [5].

The right GEA contains a well formed internal elastic membrane, but with a higher number of fenestrations than the internal thoracic artery. The mean number of fenestrations is 5/mm. However, they are smaller than fenestrations of the RA and the inferior epigastric artery and equal between 2.6 ± 0.5 μm and 3.145 ± 0.145 μm [5].

Smooth muscle cells are the predominant component of the *tunica media*, and the amount of the elastic tissue is less than in the ITA [50, 51]. There are no clearly defined elastic lamellae, but rare and individual elastic fibers are sporadically distributed between muscle cells.

These histological features make the right gastroepiploic artery prone to spasm and to the development of early atherosclerotic changes. In contrast to the ITA, the right GEA does not possess the characteristic of positive remodeling during the development of atherosclerosis [5]. In general, the ITA is unique among the grafts by this ability. Although the RAs have statistically significant increase in the media and the wall thickness, which corresponds to the internal and the external elastic laminas area increase necessary for the definition of the positive remodeling, the progressive luminal narrowing clearly demonstrates the lack of positive remodeling in the RA. As for the inferior epigastric artery, it remains to be established.

The mean thickness of the media of the right GEA varies from 168.2 to 199.8 μm and it is not changed significantly with aging. The media thickness is the highest in the RA, while the ITA, the right GEA and the inferior epigastric artery have relatively similar values of this parameter [5].

The wall thickness of this artery is 321.3 ± 69.2 μm, which is significantly higher as compared to the same parameter of the ITA [52]. According to this parameter there is no statistical significance among the right GEA and the inferior epigastric artery. At the same time, they match ideally the coronary arteries. The exception is the RA with the highest values of the wall thickness (mean 536.6 ± 114.9 μm) [5, 53].

Gender specific differences. The thickness of the intima and the media were significantly higher in the male gender [5].

Use in surgical myocardial revascularization

The use of the right GEA for coronary artery bypass surgery began with Bailey and his associates in 1966 [54]. The right gastroepiploic artery is used primarily for patients who require multiple coronary revascularizations, for grafting the left anterior descending, diagonal and circumflex coronary artery, as well as the right coronary artery. Application of this artery gained its importance with the introduction of new surgical techniques of composite grafts. According to a study, the mean rate of graft patency during the period of 7.6 months was 93% [51] or 84.5% during the 10 months follow-up [55], and according to some research, the patency of this graftin the early postoperative period is close to the patency of the ITA [45]. The results of modern research of graft patency are contradictory. Thus, it has been shown that the patency of this graft, three years after the operation, is slightly less than the patency of saphenous vein graft in the system of the right coronary artery [56], while other studies confirm a better outcome, and smaller number of complications, five years after the operation, in patients in whom the right GEA is used instead of the great saphenous vein [57].

Suma [58] has recently reported the results from the vast experience with over 1500 GEA grafts. The patency rate was 93.7% after 1 year, 86.2% after 5 years and 70.2% after 10 years. The operative mortality was 1.26%, and survival rates were 91.7% after 5 years, 81.4% after 10 years and 71.3% after 15 years.

From the standpoint of surgical anatomy, the benefits of using the right GEA is the ability to obtain graft of appropriate length and optimal diameter that fits the diameter of the coronary arteries, as well as the capacity for adequate flow. In addition, there are no gastric complications because of the artery dissection. However, a serious drawback is that the application of this artery requires intraperitoneal surgery, with its all known operative and postoperative risks, whereby only a single arterial graft can be provided [50, 51].

Conclusion

Besides the internal thoracic artery, the radial artery, the inferior epigastric artery and the right gastroepiploic artery are used for complete arterial revascularization and treatment of multivessel disease. The ultimate goal of continual basic research on arterial grafts is to find an optimal combination of grafts or new and improved grafts with morphological and functional qualities matched to provide the best therapeutic approach for each patient.

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