Ph.D. thesis

Prevascularization - A new model for the improvement of the surgical security of the esophageal resection with the help of free omental flap transplantation by microsurgical method

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1. INTRODUCTION

The esophagus is probably the most infamous organ among surgeons, therefore even these days certain types of operations with given indication are very challenging.

The anatomical features of the organ are responsible for the difficulties: hardness of approaching during operation (extraabdominal organ); the relatively thick wall of the esophagus, which is pretty easy to tear; unlike other viscera, it has no peritoneal membrane; and finally the most significant difference compared to other viscera in doing the operation is the segmental blood supply of the organ.

The difficulty of operations on organs similar to the esophagus in blood supply does not come from the location, size and tissue-build of the organ in the first place, but their special blood-supply: during surgery preparation the smaller blood vessels are damaged, so the blood supply of the organ becomes worse. This causes the higher rate of postoperative complications of this kind of organs (following esophageal resection the rate of anastomotic leakage can reach 30%).

During the 300-year-history of esophagus surgery (the first esophageal procedure was done by Baptiste Veduc in 1701 in France) the generally accepted methodology was developing empirically.

If the patient's medical condition and his state of health allows the curative surgery than the very demanding esophagus resection with high morbidity and mortality with some sort of esophagus replacement is to be done.

In case the patient's general condition does not allow difficult operation or the disease is in advanced stage only palliative solution can be applied in surgical point of view: palliative resection or some kind of bypass operation.

For the operation of certain benign diseases, as at special cases of newborns with esophageal atresia or at palliative treatment of advanced stage of esophageal cancers, the segmental resection of the esophagus could be a solution (in case of malignant diseases this works only at very early stage together with other anti-cancer treatments).

However, based on centuries of surgical experience, due to the difficulties mentioned earlier on this relatively long organ – usually 25 cm long in humans – only a 4-5 cm long part can be resected primarily (even here the risk of anastomotic insufficiency is high) and to restore the continuity of esophagus with end-to-end anastomosis.

So far surgeons have tried to improve blood-supply of esophageal anastomosis during operation and the postoperative period, as this is one of the key moves of successful operations, however, all attempts have been only partly effective.

One of the oldest methods of improving the blood-supply of given organs in the abdomen and in the retro peritoneum is covering it with omentum, which is constructed in a number of various operations these days. However, using this method extra abdominally is not very common, since it requires the transplantation of the omental-flap to the necessary area, which is a rather difficult surgical solution.

Additional problem at such procedures is that the omental-flap which is to improve the blood-supply of the organ operated is implanted at the time of the operation, so there is no time for the development of new blood vessels therefore the omentum cannot produce its protective effect in an optimal way.

In order to eliminate the problems described above, our team's aim has been to develop a new procedure for the surgical operation of esophagus resection, during which the first step would be the free transplantation of the omental-flap to the neck onto the esophagus (this process we have named prevascularization), and following the formation of the new blood supply the second step would be the resection of the esophagus (fig. 1.).

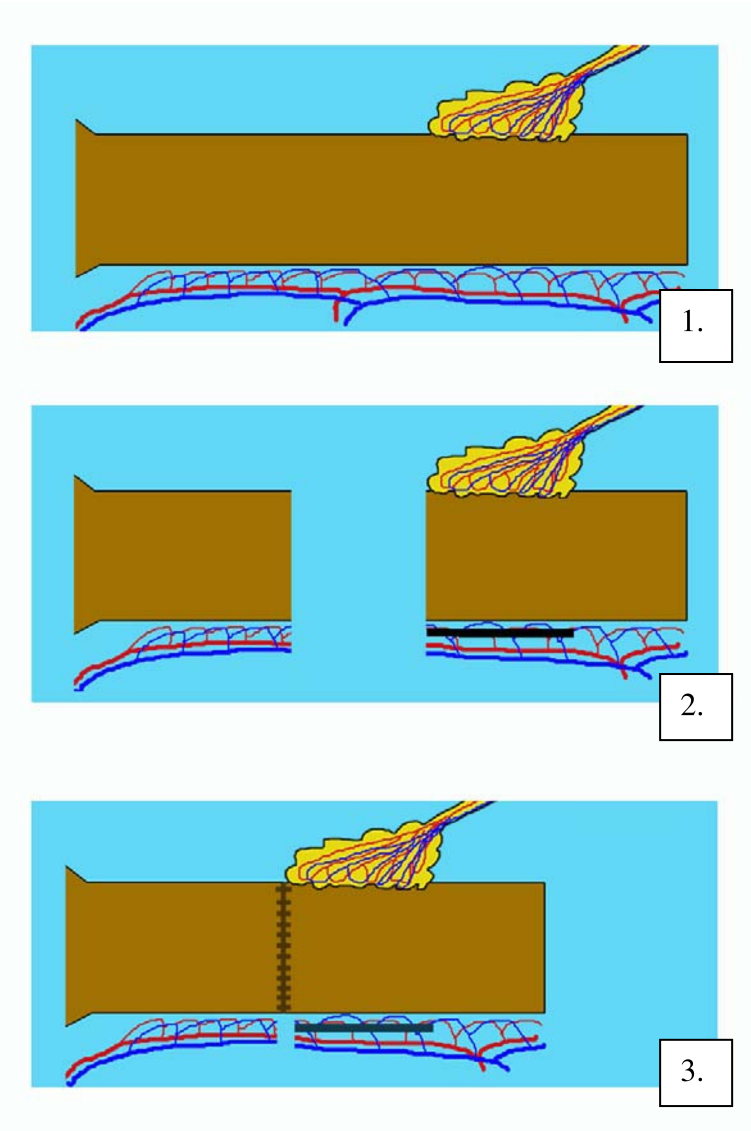

Figure 1.

Schematic illustration of newly developed esophageal resection

1./ prevacularization 2./ resection 3./ creation of the anastomosis

2. AIMS

1. Developing a method for free extraabdominal transplantation of the omental-flap on animals.
2. Elaborating the best method for omental-flap creating, harvesting.
3. Creating the necessary refrigerating-perfusing system for intraoperative curing of the omental-flap.
4. Creating the ideal solution for preventing the damage of the graft ischemia-reperfusion.
5. Working out the necessary technique of microsurgical vessel anastomosis for the transplantation of the omental-flap.
6. Developing an animal model on dogs of the esophagus resection based on fundamentally new principles.
7. Elaborating the process of postoperative treatment of the animals operated with the new method.
8. Arranging and achieving the *in vivo* and *in vitro* tests of the experiments.

3. MATERIALS AND METHODS

The series of experiments, which is the base of this dissertation, was launched in January 1 2001 with a license issued by the Debrecen University Committee of Animal Research (DEMÁB 21/2000). We have conducted the experiments fully observing the 1998. XXVIII., regulations titled „On the protection of animals".

3.1. Animals

During the majority of our experiments surgeries were carried out on healthy mongrel dogs weighing 18-22kg. During a short stage of preparation of our tests we performed operations on CD outbreed rats weighing 250-300 g.

3.2. Elaborating the surgical technique

3.2.1. Planning and preparing the recipient region

First of all we had to plan and prepare the area, where the cervical part of the esophagus can be exposing and the vessel anastomosis of freely transplanted omental-flap could be formed.

3.2.2. Microsurgical vessel anastomosis

The most difficult part of the operations was the creation of vessel anastomoses by microsurgical methods. In order to apply the most appropriate sewing technique in the experiment we tried various types of vein anastomosis.

3.2.2.1. Operations on rats

In our study we started the training of the microsurgical vessel anastomosis on rats. On 5 CD outbred rat, after transsection, we performed abdominal aorta and inferior cava vein end-to-end anastomosis, with interrupted sutures, by the help of operating microscope.

3.2.2.2. Operations on dogs

As a next step, we sewed different types (end-to-end, end-to-side, side-to-end) of vessel anastomosis on dogs. First on femoral artery and vein, next on carotid artery end on jugular vein was performed anastomosis by microsurgical technique.

3.2.3. Transplantation of the omental-flap

3.2.3.1. Harvesting of the omental- flap

After the exposure of the stomach and great omentum, both, left and right gastroepiploic vessels were investigated. During the experiment not only morphological aspects were taken into consideration to decide which side to operate, but aiming to observe the functions we have made measurement using laser Doppler flowmetry, which will be described later on.

3.2.3.2. Washing and cooling of the omental flap

Cutting through the vessels of the omental flap, cannula was attached to the omental artery (Vygon intravenous catheter, Steriflex O.R.X.0/:0.3 mm), and rinsed with room temperature physiologic saline solution in order to remove the residual blood. After isolating and removing the omental flap we cleaned it of the remaining blood and cooled it to 20 degree Celsius. We developed and created a cooling system for the purpose of cooling the flap during the operation. Affected by gravitation the perfusion solution flows out of the vessel fixed to the infusion rack so as the fitment is submerged into a liquid cooled by ice cubes. The temperature of this liquid is possible to monitor constantly. Based on the recommendations of the literature our perfusion solution contained pentoxyphillyn and vitamin-c.

3.2.3.3. Transplantation of the omental flap

The omental flap was placed onto the lateral cervical region by microsurgical method, with the assistance of an operation microscope (Leica Wild M650, Germany). Blood vessel anastomosis was made between the stem vessels and the recipient region vessels. The microsurgical phase of the operation was archived using a video camera (Panasonic CCD WV-CL 500/G) and a video picture recorder (Panasonic NV-SD435). The end-to-side anastomosis was sewed using 9/0 mono-filament, non-absorbent, synthetic (polypropylene), and running sutures (Prolene 9/0 Ethicon U.K.). First, we carried out the venous anastomosis and then the arterial anastomosis. Finally, following the appropriate positioning of the graft, we closed both operation fields.

3.2.4. Esophageal resection

14 days after the transplantation of the omental flap we opened the left lateral regions of the neck and the transplanted flap on the esophagus. We examined the viability of the transplanted flap with laser-Doppler flowmetry. Using the Boas pipe lead into the esophagus we mobilized the segment of the esophagus we intended to resect. After this we resected a full width, cylinder-shape, 2 cm long segment of the cervical part of the esophagus situated aborally of the transplanted omental flap. Continuity of the digestive tract was achieved with a manual anastomosis created with 3/0 Maxon (polyglyconate, U.S. Surgical, Division of Syneture, USA) end-to-end knotted monofil sutures. Antibiotics were done applying profilactic enrofloxacin 0,5 ml/10 kg (Baytril, Bayer AG, Germany) intramuscular. On the ninth day following the operation the animals were re-operated and exterminated.

3.3. Postoperative treatment

The postoperative treatment of the animals posed the greatest difficulty. The principles of human esophageal operations had to be modified in respect of parenteral fluid and electrolyte substitution, the use of prophylactic antibiotics (enrofloxacin 0.5 ml/10 kg (Baytril, Bayer AG, Germany) and oral feeding. Postoperative pain-killer therapy was achieved by the administration of Demalgonil (60 mg allobarbital, 400 mg aminophenaze, 600 mg urethane/2 ml, Sanofi-Synthelabo, Hungary) 1 ml intramuscularly and 1 ml subcutaneously, as demanded. On day 9 following the operation, the animals were reoperated. The integrity of the anastomosis was examined macroscopically and, after removal of the complete cervical block, histological examination (hematoxylin-eosin staining) was performed.

3.4. Laboratory examinations

On all animals that were going through the surgeries we conducted all the laboratory examinations that are usually arranged for humans in order to monitor the post-operative stage and the healing of animals and perceive possible complications on time. The animals underwent blood and laboratory tests by the following schedule: Following the first surgery in the operating room, postoperative 1., 2., 3., 5., 7., 9., 14. days. Following the second surgery postoperative 2., 4., 7., 9. days blood and laboratory tests were performed. We conducted the following laboratory examinations:

3.4.1. Hematological parameters

We examined the value of WBC, RBC, Htc, Thr, MCV, MCH, MCHC and MPV.

3.4.2. Erythrocytes deformability test

During the deformability test of erythrocytes we monitored the deformability of erythrocytes, the relative starting filtration time and relative cell transit time.

3.5. In vivo investigations of the viability of the transplanted omental flap

3.5.1. Angiography

One week after the operation of dogs on which only the omental flap transplantation had been conducted, a re-operation was performed during which we opened the left side lateral cervical region, and angiography was done with the help of an RTG image intensifier (Medicor SK-7, Hungary) after cannulation of carotid artery.

3.5.2. Methylen-blue staining

Angiography was followed by an in vivo methylene blue test (Methylthioninii chlorati, Pharmamagist, Hungary) after the cannulation of the carotid artery. After filling it with vital paint the flap and the surrounding organs were taken photography of (Konica Digital Revio KD-310z).

3.6. Investigation of the tissue microcirculation

3.6.1. Laser Doppler flowmetry

During human and animal operations, for the measuring of the tissue microcirculation laser Doppler flowmetry is a common used technique. This technique is an easy to use, non invasive, objective procedure. The laser Doppler technique indicates very sensitively the changing of the tissue microcirculation.

3.6.2. Laser Doppler flowmetry in our study

During our tests we measured the microcirculation of same points of the omental flap before isolation, after isolation, after transplantation, before the resection of the esophagus, after esophageal resection and on the end of the study. We use single chanel laser Doppler flowmeter (LD-01 Laser Doppler Flowmeter, Experimetria Kft.. U.K.-Hungary)

3.6.3. Measurement points

3.6.3.1. Measurement of the great omentum

After exposure both of the gastroepiploica stump of the great omentum, first morphologic (size, branches) and than functional tests (laser Doppler flowmetry) were done. First measuring point: right gastroepiploic stump. Second measuring point: left gastroepiploic stump.

3.6.3.2. Measurement of the isolated omental-flap

After we isolated a 10x10 cm omental flap to the blood vessel stem with a larger lumen performed laser Doppler flowmetry on the standard measuring points of the flap: point 1.: upper horizontal margin, close to stump, point 2.: upper horizontal margin, far to stump, point 3.: lower horizontal margin, far to stump, point 4.: lower horizontal margin, close to stump.

3.6.3.3. Measurement of the transplanted omental flap

After microsurgical transplantation, omental flap was checked by laser Doppler flowmetry on the same standard points after isolation.

3.6.3.4. Measurement before resection of the esophagus

14 days after omental flap transplantation, the viability of the omental flap was checked subjective and objective method, as well. Laser Doppler measuring points were: 1. intact esophagus, 2. omental flap. After flowmetry, esophagus resection was performed.

3.6.3.5. Measurement after resection of the esophagus

On the end of the study, 10 days after resection, we performed laser Doppler flowmetry again. Measuring points were the same as before esophagus resection.

3.7. Microscopic examinations

We did histological examinations on both groups of animals: those on which only the omental flap transplantation had been made and on those on which the procedure with our new method had been completely conducted. In case of the first group we examined the signs of survivability and the structural changes of the transplanted omental flap. In case of the second group we exposed and observed the changes of blood supply of the esophagus and the healing of the esophageal anastomosis. The histological examinations fall into three categories:

1. Classic hematoxylin-eosin staining
2. Immunohistochemistry tests
3. Block-examination hematoxylin-eosin staining

3.8. Statistical analysis

The data gained during our project, of which aim has been mainly the developing of a new operating technique, from the low number of surgeries conducted on test animals is not sufficient for a deep statistical analysis and coming to any conclusion based on that. We statistically processed the parameters (laboratory results, laser Doplller relative flowing units) using SigmaStat for Windows 1.0 software (SigmaStat 1.0, 1992-1994., Jandel

Scientific Co., Germany). We displayed the alteration of the hematological parameters by moving average trend lines. We performed ANOVA and Dunett's tests at the red blood cell deformability parameters. Using one-way ANOVA we analyzed the sets of data gained our laser Doppler fiber microcirculatory measurements from the flux parameters of 10 second-long, artifact free, representative segments of laser Doppler flux curves recorded at each operation during.

4. RESULTS AND CONSEQUENCES

During our experiments we conducted 24 operations using the methods detailed earlier on 12 dogs and 5 rats. We did not have major complications and all animals survived the interventions. On concluding the experiments we exterminated all animals as instructed by the regulations of the earlier mentioned animal protection laws.

4.1. Results of the transplantation of the omental flap

4.1.1. Harvesting of the omental flap

Best way to expose the omentum, was performing upper median laparotomy.

4.1.2. Washing and cooling of the omental flap

The cooled graft can stand a longer ischaemic time without injury, so in our model, we cool the omental flap we want to transplant to 20 degrees Celsius with the assistance of intraoperative perfusion. For the purpose of defense against ischaemic-reperfusion damage to the omentum, the perfusing solution contains vitamin C and pentoxyphillin

4.1.3. The microsurgical technique of the vessel anastomosis

The veins of the omental flap and the recipient region of the middle-size test animals were so small that the anastomosis and the final placement of the omental flap to the esophagus could be conducted only via microsurgical methods using operation microscope.

In case of the anastomosis first, we place a stich in the two poles of the two vessels we wish to stich up, then we carry out running sutures to the end of the opposite side pole, finally, with the other suture from this pole on the outside wall we stich the anastomosis. Here the timing of the making of anastomoses is critical as from then on the cooling of the flap can be done only externally, until the reperfusing of the flap.

4.2. Result of the work out of the resection of prevascularized esophagus

4.2.1. Recipient region

During our experiments the left side lateral cervical region proved to be found the best recipient area. Vessels of this region (the recipient artery was the common carotid artery, and the recipient vein its satellite vein. If the diameter of the latter was not appropriate, the external jugular vein was used as recipient) are easy to use for creating end-to-side anastomosis. The size and location of these veins always proved to be appropriate for the purpose of transplantation. In some cases the external jugular vein was too short to get it end-to-side fashion. In those cases the vein was cut higher position and we put it through a tunnel, thus making it eligible for the proper anastomosis.

4.2.2. Transplantation of the omental flap

All animals survived the short-term survival period and there were no general complications in result of the operation, 5 out of 4 of the transplanted flaps survived the period in question, one flap thrombotized due to technical reasons (angulation of the vein of the omental flap when it was fixed in its final position).

4.2.3. Result of the resection of the prevascularized esophagus

Using the methods elaborated by us, the duration of the operation was reduced to 2 hours from the original 4 hours and the time of vessel anastomosis (artery and vein) to half an hour from 1 hour. The average graft ischemia time was 45 minutes. We conducted the angiography, methylen-blue staining and the histological examinations at the first group of animals 3 occasions after one week following the transplantation, at the second group of animals 2 times after 14 days following the transplantation. At the latter the tests were part of the full surgical experiment.

4.2.4. Result of the postoperative treatment after resection of the esophagus

In comparison with human esophageal operations, we had to solve an appreciable number of technical problems during and after the series of operations. The performance of the operations was basically influenced by the fact that the area of the operation could not be drained. The postoperative treatment of the animals posed the greatest difficulty. The principles of human esophageal operations had to be modified in respect of parenteral fluid and electrolyte substitution, the use of prophylactic antibiotics and oral feeding.

4.3. Investigation of the viability of the omental flap

4.3.1. Angiography

We found that due to the considerably small size of the arteries in the flap, the angiography conducted routinely on humans is not suitable to assess the survivability of the transplanted flap.

4.3.2. Methylen-blue staining

We found that during the methyl-blue staining the transplanted flap turned to blue in a very short time. We found that the method in vivo is inadequate for the verification of the delicate structural changes that are required to assess survivability.

4.3.3. The results of Laser Doppler flowmetry

We performed Laser Doppler flowmetry short term survivability examinations at two animals, and both flaps monitored by Doppler flowmeter survived. Based on the data gained during the examination of two animals we can confirms that the value of rBFU is less at the measurement points far from stump. This fact shows the greatest reduction in flow during the operations. On comparing the flow values of the measurement points during the stages of the series of operations we found that the rBFU is less at the points furthest from the stump of the flap and the least at the 4. measurement point, practically all along.

4.3.4. Results of the laboratory examinations

Following the first operation during the first 5 post-operative days the hematrocit was constantly decreasing and then remained on the same level until the end of the experiments. Similar pattern was shown at the red blood cell number and the hemoglobin level, as well while average red blood cell volume did not change. The number of leukocytes significantly increased on the first two postoperative days following the first operation, then it decreased. However, it increased again on the second postoperative week. After the II. operation, though the number of leukocytes was constantly dropping. In the beginning the thrombocyte level behaved similarly to the leukocytes level, namely it was decreasing during the first week following the I. operation and was slightly increasing in the second week, however, after the II. operation we found that the thrombocyte level increased substantially.

The relative cell transit time (RCTT) was only slightly extended at the end of the I postoperative period, while at the end of the II postoperative period the deformability was reduced considerably, as the cell transit time was significantly higher compared to the base, that is the result of the I postoperative period.

4.3.5. Results of microscopic examinations

4.3.5.1. Hematoxylin-eosin staining of the prevascularized intact esophagus

With the hematoxylin-eosin staining method the viability of the omental flaps, their post-operative survival and the possible circulatory complications could be monitored very effectively. Also, the changes in the tissue structure of the flap itself could be followed by this method. The hematoxylin-eosin staining indicated that the tissue structure of the transplanted omental flap was partially transformed, the fat cells were degenerated and most of them were absorbed. Furthermore myofibroblast proliferation started in the structure of the omentum and endothelial cells started to appear there and small capillaries were created.

4.3.5.2. Immunohistochemistry of the prevascularized intact esophagus

With the indirect immunohistochemistry method and using CD34 antibody the appearance of endothelial cells and the proliferation of the capillaries was demonstrated. Based on our examinations this method is the most effective to prove the development of small veins and capillaries in the extra-abdominally transplanted omental flap, which was mentioned in earlier publications, as well.

4.3.5.3. Hematoxylin-eosin staining of the prevascularized and resected esophagus

The block histological examination of the prevascularized and resected esophagus anastomosis confirmed our starting hypothesis, that the transplanted omental flap grew into the tissue structure of the esophagus.

5. SUMMARY OF MOST IMPORTANT RESULTS AND CONSEQUENCES

1. Elaborated a new method, which takes into account objective parameters as well, to harvest omental flap on dogs.
2. Developed and created a refrigerating-perfusion system, which enables us to effortlessly cool and perfuse the isolated omental flap during transplantation. To prevent the damage of the graft ischemia-reperfusion we used a perfusion solution developed experimentally to perfuse the graft to be transplanted.
3. We developed the appropriate technique of microsurgical vessel anastomosis to transplant omental flap on dog modifying the technique of Remie and colleagues.

4. We created an animal-model for a fundamentally new method of segmented esophageal resection, during which the resection is accomplished in two steps: first, the omental flap is transplanted to the cervical segment of the esophagus – we called this process prevascularization – and 14 days afterwards the resection and anastomosis is conducted on the previously affected esophagus with improved blood-supply.
5. We developed the method of post-operative treatment on dogs following the new type of esophageal resection.
6. This is the first time we applied laser Doppler flowmetry for the intraoperative monitoring of tissue microcirculation in connection with omental flap transplantation.
7. With the applied histological tests on the first hand we were able to monitor the transformation of the tissue structure of the transplanted omental flap and on the other hand we could highlight the supportive effects of the omental flap on the circulation of the esophagus: haematoxylin-eosin staining for the structural transformation of the flap, indirect immunhistochemistry for the better demonstration of newly developed capillaries, and finally block histological examination for the most effective monitoring of the healing of the esophageal anastomosis.

LIST OF PUBLICATIONS

In extenso publications related to thesis

1. Pap-Szekeres J., Cserni G., Furka I., Svébis M., Cserni T., Bráth E., Németh N., Mikó I.: New operative technique for transplantation of a free omental graft in dogs. Microsurgery 2003;23:414-418. IF: 0,812
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Impact factor: 1,609

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Impact factor: 2,425

Cumulative impact factor of the *in extenso* publications: 4,846

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Cumulative impact factor of published abstracts: 2,900

CUMULATIVE IMPACT FACTOR: 7,746 (*in extenso*: 4,846 + abstracts: 2,900)

Oral and poster presentations

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