<https://helda.helsinki.fi>

Intraoperative processing and epicardial transplantation of autologous atrial tissue for cardiac repair

Lampinen, Milla

2017-09

Lampinen , M , Nummi , A , Nieminen , T , Harjula , A , Kankuri , E & AADC Consortium
2017 , ' Intraoperative processing and epicardial transplantation of autologous atrial tissue
for cardiac repair ' , Journal of Heart and Lung Transplantation , vol. 36 , no. 9 , pp.
1020-1022 . <https://doi.org/10.1016/j.healun.2017.06.002>

<http://hdl.handle.net/10138/297946>

<https://doi.org/10.1016/j.healun.2017.06.002>

publishedVersion

Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.

This reprint may differ from the original in pagination and typographic detail.

Please cite the original version.

CASE ANECDOTES, COMMENTS AND OPINIONS

Intraoperative processing and epicardial transplantation of autologous atrial tissue for cardiac repair

Milla Lampinen, PhD,^a Annu Nummi, MD,^b
 Tuomo Nieminen, MD, PhD,^{c,d}
 Ari Harjula, MD, PhD,^b Esko Kankuri, MD,
 PhD^a and on behalf of the AADC
 Consortium¹

From the ^aDepartment of Pharmacology, Faculty of Medicine, University of Helsinki, Helsinki; ^bHeart and Lung Center, Helsinki University Hospital, Helsinki; ^cDepartment of Internal Medicine, Helsinki University Hospital, University of Helsinki, Helsinki; and the ^dDepartment of Internal Medicine, South Karelia Central Hospital, Lappeenranta, Finland

We present the production and clinical application of autologous atrial micrografts during coronary artery bypass grafting (CABG). Micrografts are isolated from otherwise discarded atrial appendage (AA) tissue and are combined with fibrin gel¹ and a decellularized small intestinal submucosa (SIS) matrix sheet (Figure 1a).² The technique—mechanical tissue processing, preparation of the transplant, and its topical application with a matrix sheet—is performed during CABG (Figure 1a, b). The protocol is provided in Appendix 1 (available online at www.jhltonline.org).

The transplant production takes approximately 30 minutes, whereas the isolation of the micrografts takes approximately 8 minutes for an average size tissue piece. In a set of samples received from the CABG operation, the average weight of AA tissue was 0.895 ± 0.45 g ($n = 15$). Mechanical isolation yields cells and micrografts, cellular aggregates attached to their matrix (Appendix 2A-D and Movie Appendix 2, online). Cell yield was $9.76 \times 10^6 \pm 0.53$ /g of tissue ($n = 11$), and cellular viability was 90.6% ($n = 7$).³ After isolation, micrografts are spread onto the SIS sheet. A slowly gelling matrix of fibrin diluted with cardioplegia is laid over the micrografts. The graft is kept metabolically inhibited on a cooling plate until transplantation.

A 64-year-old man diagnosed with coronary artery disease and heart failure was scheduled for elective bypass grafting. He had exercise dyspnea, and his angiogram showed 3-vessel disease. Our clinical safety and feasibility study (ClinicalTrials.gov identifier NCT02672163) enrolled

the patient after assessing the patient's eligibility and receiving his written informed consent.

In the beginning of the operation, a small piece of right atrial appendage was excised while the right atrium was being cannulated (Figure 1b, panels C–D) and was used for preparation of the micrografts. After the 3 bypass anastomoses were completed, but before reperfusion, the micrograft transplant was placed on the anterior wall of the left ventricle (Figure 1b, panel F) on the scar area identified in the preoperative magnetic resonance imaging. The sheet was sutured to the myocardial surface with minimal disturbance to the contracting muscle (Figure 1b, panels F–G).

The patient recovered well from the operation and was discharged from the hospital after 7 days. At the 3-month postoperative follow-up, the patient was practicing regular exercise and had returned to work. Magnetic resonance imaging at 6 months showed markedly improved movement (Movies A and B, online) and ventricular wall thickening (Figure 2) in the treated infarcted scar area.

The use of AA as the cell source provides advantages over conventional cell therapy procedures.^{4,5} Firstly, cells in the micrografts stay attached to their tissue-specific extracellular matrix. Secondly, cardiac tissue-derived cell population heterogeneity can serve as the basis for cardiac tissue arrangement and give rise to an array of paracrine signals. The progenitor and stem cell pools in the AA help drive neovascularization and myocardial tissue-type differentiation directly or via paracrine effects.⁶

The AA-derived micrografts can be further modified by or supplemented with, for example, additional matrix components, paracrine factors, microRNAs, microvesicles or microparticles, or drugs.⁵ The micrografts can also be used as vehicles for gene therapy.⁷ Taken together, the AA micrograft transplant holds great potential to serve as the future first-line cardiac cellular therapy.

Disclosure statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

This research was supported by the Finnish State Grant (TYH Y2016SK013), the Finnish Foundation for Cardiovascular Research, and the Finnish Funding Agency for Technology and Innovation (TEKES).

Antonio Graziano contributed to the development of the mechanical tissue processor Rigenara at HBW srl. The authors had freedom of investigation and full control of the planning of the study, methods used, outcome parameters and results, analysis of data and writing the report.

¹AADC Consortium members are listed in [Supplementary material](#), available online.

Figure 1 (a) Cardiac micrograft production in conjunction with bypass surgery. The atrial appendage is processed into micrografts, combined with fibrin and extracellular matrix sheet, and the graft is transplanted epicardially on the injured myocardium. (b) Single operation atrial appendage micrograft therapy. (A) The instrument table setup for cell transplant production with (B) the bypass operation. When the patient is prepared for on-pump surgery by cannulating the right atrium, (C) the atrial appendage (*black arrow*) is first occluded with a clamp and sutures, after which (D) a piece of atrial appendage tissue (*black arrow*) is cut and (E) collected for cell-micrograft isolation and composition of the graft. (F and G) After revascularization therapy is finished, the graft (*white arrow*) is transplanted epicardially. All persons appearing in the figures provided their written permissions for publication of their photographs.

Figure 2 Cardiac magnetic resonance imaging (MRI) was performed preoperatively and at 6 months follow-up. An akinetic area (white arrow) was seen at the basal area of the lateral left ventricular wall in the patient. This could be seen both in long and short axis views (Figures A and B). This area was determined to be the site of implantation of the cardiac patch. Six months after revascularization and cardiac patch implantation (Figures C and D), the treatment area showed significant improvement in both local wall thickness and systolic thickening.

The authors thank research nurse Liisa Blubaum for her excellent help in development of the AA-derived transplant and Eila Perttula, Riikka Hänninen, Kati Helleharju, Mariitta Salmi, Veikko Huusko, Olli Valtanen, and Sole Lätti for their contributions to the development process.

Appendix A. Supporting information

Supplementary data are available in the online version of this article at www.jhltonline.org.

References

1. Spotnitz WD. Fibrin sealant: the only approved hemostat, sealant, and adhesive—a laboratory and clinical perspective. *ISRN Surg* 2014;2014: 203943.
2. Mosala NZ, Poncelet A, de Kerchove L, et al. Small intestinal submucosa extracellular matrix (CorMatrix®) in cardiovascular surgery: a systematic review. *Interact Cardiovasc Thorac Surg* 2016;22: 839-50.
3. Trovato L, Monti M, Del Fante C, et al. A new medical device Rigenacons allows to obtain viable micro-grafts from mechanical disaggregation of human tissues. *J Cell Physiol* 2015;230:2299-303.
4. Pätälä T, Lehtinen M, Vento A, et al. Autologous bone marrow mononuclear cell transplantation in ischemic heart failure: a prospective, controlled, randomized, double-blind study of cell transplantation combined with coronary bypass. *J Heart Lung Transplant* 2014;33: 567-74.
5. Lampinen M, Vento A, Laurikka J, et al. Rational autologous cell sources for therapy of heart failure—vehicles and targets for gene and RNA therapies. *Curr Gene Ther* 2016;16:21-33.
6. Le T, Chong J. Cardiac progenitor cells for heart repair. *Cell Death Discov* 2016;18:16052.
7. Kankuri E, Harjula A. Cells and gene therapy—“do you like green eggs and ham? *Curr Gene Ther* 2016;16:3-4.