Research Paper

First-in-man Safety and Efficacy of the Adipose Graft Transposition Procedure (AGTP) in Patients With a Myocardial Scar

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A B S T R A C T

Background: The present study evaluates the safety and efficacy of the Adipose Graft Transposition Procedure (AGTP) as a biological regenerative innovation for patients with a chronic myocardial scar.

Methods: This prospective, randomized single-center controlled study included 10 patients with established chronic transmural myocardial scars. Candidates for myocardial revascularization were randomly allocated into two treatment groups. In the control arm (n = 5), the revascularizable area was treated with CABG and the non-revascularizable area was left untouched. Patients in the AGTP-treated arm (n = 5) were treated with CABG and the non-revascularizable area was covered by a biological adipose graft. The primary endpoint was the appearance of adverse effects derived from the procedure including hospital admissions and death, and 24-hour Holter monitoring arrhythmias at baseline, 1 week, and 3 and 12 months. Secondary endpoints of efficacy were assessed by cardiac MRI.

Findings: No differences in safety were observed between groups in terms of clinical or arrhythmic events. On follow-up MRI testing, participants in the AGTP-treated arm showed a borderline smaller left ventricular end systolic volume (LVEVS; p = 0.09) and necrosis ratio (p = 0.06) at 3 months but not at 12 months. The AGTP-treated patient with the largest necrotic area and most dilated chambers experienced a noted improvement in necrotic mass size (−10.8%), and ventricular volumes (LVEDV: −55.2 mL and LVEVS: −37.8 mL at one year follow-up) after inferior AGTP.

Interpretation: Our results indicate that AGTP is safe and may be efficacious in selected patients. Further studies are needed to assess its clinical value. (ClinicalTrials.org NCT01473433, AdiFlap Trial).

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1. Introduction

Cardiovascular disease remains the most common cause of mortality worldwide, accounting for more than 17 million deaths annually (Anon., 2011). Myocardial infarction (MI) leads to irreversible myocardial sequelae, often causing debilitating symptoms and shortening life span. Recently, biological regenerative innovations have been introduced as promising therapeutic options (Soler-Botija et al., 2012; Gálvez-Montón et al., 2013a; Prat-Vidal et al., 2014).

Cardiac fat contains a population of mesenchymal-like progenitor cells capable of differentiating into cells that closely resemble cardiomyocytes, both morphologically and molecularly. In murine MI models, these cells improved cardiac function parameters and promoted local neoangiogenesis under hypoxia (Bayes-Genis et al., 2010). The adipose tissue surrounding the heart and pericardium may serve as an autologous biological matrix for salvaging injured myocardium. The Adipose Graft Transposition Procedure (AGTP) uses patient’s existing cardiac fat directly, placing it over the myocardial infarcted zones, rather than explanting a cardiac adipose biopsy to retrieve the cells (Gálvez-Montón et al., 2011; Gálvez-Montón et al., 2013b). In the

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acute MI porcine model, functional analyses showed an improvement in LVEF in the AGTP-treated arm five-fold higher than untreated animals (Gálvez-Montón et al., 2011). In the chronic MI porcine model, morpophometry revealed a 34% reduction in left ventricular infarct area of AGTP-treated relative to control animals (Gálvez-Montón et al., 2013b). These preclinical studies in a large mammal model suggest that AGTP may be an effective post MI treatment for patients. Accordingly, a prospective randomized trial was set up to assess safety and efficacy of AGTP in patients with a myocardial scar.

2. Patients and Methods

2.1. Patients

The study included 10 candidates for myocardial revascularization with an established chronic transmural myocardial scar, from January 2012 to November 2013. Inclusion criteria included patients ≥18 years of age, with an established transmural MI (minimum three months old) anatomically non amenable for surgical revascularization, and candidates for coronary artery bypass graft (CABG) surgery of other arteries non responsible for the transmural scar. A non-revascularizable area was defined as a chronic transmural necrosis detected by means of late gadolinium enhancement >70% of myocardial thickness on MRI.

Exclusion criteria were: severe valvular disease apt for surgery, candidates to surgical ventricular remodeling, contraindication for MRI, extra-cardiac disease with life expectancy <1 year, severe renal or hepatic insufficiency, previous cardiac surgery, very high surgical risk by EuroSCORE (>8), and pregnant or breastfeeding women.

2.2. Study Design and AGTP Intervention

This study was a prospective, single-center, randomized controlled phase I–II clinical trial (ClinicalTrials.gov number NCT01473433, AdiFLAP Trial). It was designed and implemented in accordance with the Declaration of Helsinki; informed consent was obtained from all participating patients.

Enrolled patients were randomly allocated in 2 arms (Fig. 1):

- Control arm (n = 5): Patients in whom the revascularizable area was treated with CABG and the non-revascularizable area was left untouched.
- AGTP-treated arm (n = 5): Patients in whom the revascularizable area was treated with CABG and the non-revascularizable area was covered by an autologous pericardial adipose graft. Fig. 2 summarizes the steps of the AGTP intervention. First, to obtain the graft, the pericardial adipose tissue was detached with its vascularization intact (depending on scar location, the adipose tissue was detached from the left or the right side of the pericardium as needed); next, after pericardiotomy, the vascular adipose graft was gently positioned to ensure full coverage of the necrotic zone; finally, to secure the flap, the edges were adhered to bordering healthy myocardium with commercially available cyanoacrylic-based surgical glue (Glubran®2, USA) (Gálvez-Montón et al., 2011; Gálvez-Montón et al., 2013b; Bagó et al., 2013; Roura et al., 2015).

The clinical cardiologist handling postsurgical care and the MRI specialist were both blind to the participants’ treatment. Study visits consisted of a baseline visit (obtained informed consent and performed clinical assessment, including MRI), surgical intervention, and follow-up visits at one week (clinical assessment), three and 12 months (clinical assessment including MRI) after procedure.

Safety of the procedure was evaluated by the presence of major clinical events including hospital admissions and death, and by the results of a 24-hour Holter monitor test done at each study visit to assess arrhythmias. Efficacy was assessed by left ventricular ejection fraction (LVEF), cardiac output (CO), stroke volume (SV), end-diastolic wall mass (EDWM), left ventricular end-diastolic (LVEDV) and end-systolic volume (LVESV) by means of cardiac-MRI. NTproBNP, troponin I (TnI), NYHA functional class and Framingham derived clinical score were also assessed.

2.3. Cardiac MRI Data Acquisition and Analysis

All imaging were performed in a state-of-the-art 1.5 T clinical imaging system (Avanto; Siemens Medical Imaging, Erlangen, Germany) with the patient in the supine position and a 16-element phased-array coil placed over the chest. Images were acquired during breath-holds with ECG gating. We used a segmented k-space steady-state free-precession sequence [RT 44.70 ms; echo time 1.26 ms; flip angle 78; matrix 272; spatial resolution (1.3–1.5)×(1.3–1.5) × 8 mm depending on the field of view] for cine imaging in parallel short-axis (contiguous slices of 8-mm thickness covering from base to apex) and 3 long-axis views of the left ventricle. Delayed enhancement images were acquired with a segmented gradient-echo inversion-recovery sequence [RT (600–800) ms depending on the cardiac heart rate; echo time 3.24 ms; flip angle 25; matrix 256; spatial resolution 1.3 × 1.3 × 8 mm] at matching cine-image slice locations 10 to 20 min after intravenous gadolinium-DTPA administration (0.20 mmol/kg; Gadovist, Bayer Schering Pharma AG, Berlin, Germany) (Simonetti et al., 2001). We optimized the inversion time to null the normal myocardium and adjusted views per segment and trigger delay according to the patient’s heart rate. Native and post contrast cardiac T1 mapping was calculated using a modified Look–Locker inversion recovery sequence (MOLLI) in a short axis view at the infarct level (Moon et al., 2013; White et al., 2013; Messroghli et al., 2004, 2007).

All images were reviewed and analyzed off-line with a specialized post-processing software (QMass-MR, v.7.0; Medis Medical Imaging).
by an independent core lab, which collected and interpreted all imaging data blinded to the clinical data and outcome (J.A.S., A.R.: ICICORELAB, Valladolid, Spain; A.T.). LV endocardial border (papillary muscles were excluded) were manually traced on all short-axis cine images at the end-diastolic and end-systolic frames to determine the LV end-diastolic and LV end-systolic volumes, respectively. LV mass was calculated by subtracting the endocardial volume from the epicardial volume at end diastole and then multiplying by the tissue density (1.05 g/mL) (Kramer et al., 2008).

The endocardial and epicardial contours on delayed enhancement images were also outlined manually. ROIs were then manually traced in the hyperenhanced area at place of maximum signal intensity and in the normal-appearing remote myocardium. As previously described, the areas of hyperenhancing myocardium were then automatically segmented by using a full-width at half-maximum (FWHM) algorithm (Flett et al., 2011; Amado et al., 2004). Two corrections were required for all automated ROIs. First, microvascular obstruction (defined as hypointensity within a hyperintense region in patients with infarctions) was adjusted to be included as late gadolinium enhancement (LGE) if present. Second, any obvious blood pool or pericardial partial voluming and artefacts were further removed from the ROI.

Scar volume for each slice was calculated as: area scar \times slice thickness. The scar mass was expressed as total scar volume \times 1.05 g. The scar percentage of myocardium was also expressed as a percentage of the total myocardial volume: volume scar / volume myocardium \times 100.

T1 mapping derived extracellular volume (ECV) of the necrotic area was estimated using the native and post-contrast myocardial and blood pool T1 maps, accounting for the patient hematocrit at the time of exploration. The T1 map ROI was manually traced covering the entire necrotic area avoiding any blood pool or pericardial partial voluming or artefact. Moreover, areas of microvascular obstruction or fatty infiltration were excluded from the T1 mapping calculation in order to avoid any bias (Kellman et al., 2015).

2.4. Statistical Analysis

Descriptive analyses were performed at the first step. Categorical variables were described by frequencies and percentages. Continuous variables were described by means and standard deviations or medians and interquartile ranges in cases of skewed distribution. Differences between groups were compared using Student’s t-test or one-way ANOVA for multiple comparisons, with Tukey’s test for post hoc analyses. The comparison of continuous variables between groups was performed using analysis of variance for unpaired data once normality was demonstrated (Kolmogorov–Smirnov test); otherwise, a nonparametric test (Mann–Whitney or Kruskal–Wallis test) was used. MRI data were analyzed as repeated measures using ANOVA with Greenhouse–Geisser correction. A 2-sided p < 0.05 was considered significant. Statistical analyses were performed using SPSS statistical package 19.0.1 version (SPSS Inc, Chicago, IL, USA).

2.5. Role of the Funding Source

The funding sources had no such involvement.

3. Results

Ten patients were included, randomly allocated to control (n = 5) or AGTP-treated (n = 5). One patient in the control group (Patient #2) was excluded after randomization because of MRI claustrophobia, resulting in a total sample size of n = 9. All patients were men and there were no significant differences between groups in clinical
ECC: extracorporeal circulation; AGTP: Adipose Graft Transposition Procedure.

Overall, we did not observe significant differences between the AGTP-treated and control patients assessed by MRI are shown in Fig. 3. Table 4 shows MRI cardiac function data.

In arrhythmia prevalence, although the number of supraventricular tachycardias reduced (Table 3).

There were no differences in hospital admissions during follow-up identifications between groups.

Data expressed in mean and standard deviation.

AGTP: Adipose Graft Transposition Procedure; HR: heart rate; NYHA: New York Heart Association; NTproBNP: N-terminal pro-B-type natriuretic peptide; ECG: electrocardiogram; TnI: Troponin I; LVEF: left ventricular ejection fraction; LVESV: left ventricular end systolic volume; LVEDV: left ventricular end diastolic volume; CD: cardiac output.

variables, nor in variables related to disease severity or surgical risk (Table 1).

The same surgeon performed all interventions (M.C.). Patency of all grafts was confirmed and no adverse events were detected during surgery. Table 2 summarizes the surgical characteristics of study patients and Video 1 shows an inferior AGTP.

No differences in procedure safety were observed between groups (Table 3). Unrelated to the procedure, one patient died in the AGTP-treated arm after seven months due to colonic adenocarcinoma. There were no differences in hospital admissions during follow-up identified between groups. One hospital admission was registered in each group: in the control arm due to symptomatic hypotension and in the AGTP-treated arm for colonic resection, respectively. 24-hour Holter monitoring during 1-year follow-up showed non-significant reductions in the extracellular space from baseline to 3-month follow-up in AGTP-treated versus control patients (~4.5% vs. ~1.1%, respectively; p = 0.53). No differences in NTproBNP, TnI, NYHA functional class and Framingham-derived clinical score were found between groups.

However, Greenhouse–Geisser analyses, which include inter- and intra-individual changes over time, did reveal a trend for smaller LVESV (p = 0.09) and necrosis ratio (p = 0.06) in the AGTP-treated arm at three months. Infarct site-derived T1 mapping extracellular volume (ECV) estimation revealed no significant reduction in the extracellular space from baseline to 3-month follow-up in AGTP-treated versus control patients (~4.5% vs. ~1.1%, respectively; p = 0.53). No differences in NTproBNP, TnI, NYHA functional class and Framingham-derived clinical score were found between groups.

One patient in the AGTP-treated arm experienced a remarkable improvement after inferior AGTP (Fig. 4). At the beginning of the study, he had the largest necrotic area (LV necrotic mass: 33.2%) and the most dilated ventricular chambers (LVEDV: 315.1 mL; LVESV: 218.5 mL) of all participants; 3 months after AGTP treatment LV necrotic mass was reduced by 4.4%, LVEDV by 31.9 mL, and LVESV by 23.8 mL. After one-year follow-up, these numbers had decreased further to 10.8%, 55.2 mL, and 37.8 mL for LV necrotic mass, LVEDV, and LVESV respectively. Remarkably, Q waves vanished from leads I, II and III in the follow-up ECGs (Fig. 4).

4. Discussion

The results of this pilot study in a prospective cohort indicate that AGTP is a safe procedure that may be efficacious in selected patients. Given its autologous nature and ease of implementation, the translation of the AGTP technique to clinical practice should not be hampered by technical difficulties, economic restrictions, nor ethical or social considerations.

The mechanism of the positive effects of this biological innovation is uncertain, but one possibility is the establishment of vascular connections between the adipose graft and the underlying myocardium as previously demonstrated in the swine MI model (Bayes-Genis et al., 2013). There are few accepted techniques of vascularizing a damaged heart. In brief, direct methods such as the simple insertion of an internal mammary artery into the myocardium through a hole (Unger et al., 1990)

### Table 1
Baseline clinical and MRI variables of the studied population.

| Patient | EuroSCORE | Logistic EuroSCORE | Logistic EuroSCORE II | ECC | ECC time | Ischemia time | N° grafts | Study arm | AGTP location |
|---------|------------|--------------------|-----------------------|-----|----------|--------------|-----------|-----------|---------------|
| 1       | 3          | 2.40%              | 1.16%                 | Yes | 92       | 62           | 3         | AGTP      | Inferior      |
| 2       | 4          | 3.51%              | 2.39%                 | No  | –        | 0            | 1         | Control   | –             |
| 3       | 5          | 2.07%              | 0.95%                 | Yes | 81       | 57           | 3         | AGTP      | Inferior      |
| 4       | 6          | 3.76%              | 1.80%                 | Yes | 89       | 44           | 3         | Control   | –             |
| 5       | 7          | 10.06%             | 3.56%                 | No  | –        | 0            | 1         | AGTP      | Inferior      |
| 6       | 8          | 2.89%              | 2.44%                 | Yes | 44       | 32           | 2         | Control   | –             |
| 7       | 9          | 4.38%              | 3.05%                 | Yes | 70       | 32           | 2         | AGTP      | Superior      |
| 8       | 10         | 1.51%              | 0.58%                 | Yes | 60       | 42           | 2         | Control   | –             |

ECC: extracorporeal circulation; AGTP: Adipose Graft Transposition Procedure.

* Percentage of predicted operative mortality for patients undergoing cardiac surgery by logistic EuroSCORE I and II formulas.
or transmyocardial perforation created with lasers mimicking the sinu-
soids observed in reptilian hearts (Stone et al., 2002) have not demon-
strated a clear-cut clinical benefit. In contrast, indirect revascularization
of damaged organs with vascular grafts has been successfully achieved
(Rocha et al., 2007; Motegi et al., 2007). Previous reports indicate that
following AGTP new microvessels developed, bridging the interface
between the adipose vascular graft and adjacent myocardium
(Gálvez-Montón et al., 2011; Gálvez-Montón et al., 2013b) thus enabling
an exchange of nutrients and progenitors between the biological adipose
graft and the underlying myocardial scar.

It is unclear whether the adipose-derived progenitor cells exert a
role in the beneficial effect of the AGTP. Recent data suggested that car-
diac adipose-derived progenitors have an inherent cardiac-like pheno-
type and may support heart homeostasis, perhaps as a cell reservoir
for renewing myocardial tissue. Indeed, in vivo studies in murine
models have clearly shown that cardiac adipose-derived progenitors
displayed a beneficial effect in the context of MI. Cell transplantation re-
sulted in improved cardiac function parameters and was associated
with a significant increase in infarct-related wall thickness (Bayes-
genis et al., 2010). In pre-clinical studies in the porcine model, cell traf-
ficking from the adipose graft to the infarcted myocardium was also ob-
served (Gálvez-Montón et al., 2011). Finally, adipokines liberated by
the graft may exert a positive local effect and should be considered as an
alternative mechanism. Many studies have described the myocardium
and perivascular adipose tissue as well-known sources of hormones,
which might exert important autocrine, paracrine, and endocrine ef-
facts (Ahima and Flier, 2000). Indeed, evidence suggests that adipose-
derived hormones can offer cardio-protective effects, including attenu-
ation of cardiomyocyte apoptosis, reduction of infarct size, and modula-
tion of collagen I/III ratios (Sweeney, 2010).

Identification of AGTP responders is an unresolved challenge, but
may ultimately be the key to explaining the case of the AGTP-treated

### Table 4

|                      | AGTP-treated |                  |                  | Control |                  |                  |
|----------------------|--------------|------------------|------------------|---------|------------------|------------------|
|                      | Baseline     | 3 months         | 12 months        | Baseline | 3 months         | 12 months        |
| Necrosis mass, gr    | 33.9         | 32.9             | 30.0             | 25.2     | 23.8             | 22.4             |
| Necrosis ratio, %    | 22.3         | 20.1             | 19.3             | 18.4     | 20.2             | 17.8             |
| LVEF, %              | 41           | 42               | 47               | 42       | 47               | 46               |
| LVESV, ml            | 139.6        | 131.9            | 114.9            | 127.8    | 99.2             | 104.6            |
| LVEDV, ml            | 219.8        | 218.0            | 202.4            | 212.2    | 187.7            | 194.6            |
| CO, L/min            | 5.0          | 5.5              | 5.8              | 5.1      | 5.9              | 5.5              |
| SV, ml               | 80.2         | 87.3             | 87.5             | 84.4     | 88.5             | 90.1             |

Data expressed in mean and standard deviation. No statistically significant differences were observed.

AGTP: Adipose Graft Transposition Procedure; LVEF: left ventricular ejection fraction; LVESV: left ventricular end systolic volume; LVEDV: left ventricular end diastolic volume; CO: cardiac output; SV: stroke volume.
A Phase II graft may be a safe alternative in patients with chronic myocardial ne-
volution translates to superior cardiac function with longer follow-up. This study provides evidence that use of an autologous vascular adipose matrix wrapping the infarcted area. However, the derived T1 mapping ECV estimation may reflect an improvement in scar composition. Furthermore, future MRI software refinements may allow a more precise definition of the adipose graft surrounding the heart.

At present, cell therapy has been the most tested biological approach for cardiac regeneration/recovery in humans. Cell therapy is safe, but with controversial benefits measured in surrogate endpoints such as LVEF. The recent multicenter, prospective, randomized open-label TECAM trial evaluated three different bone marrow-derived stem cell approaches in MI (intracoronary bone-marrow mononuclear cell — BMNC; injection; mobilization with G-CSF; and both BMNC injection plus G-CSF), none of which resulted in improvement of LVEF or volumes compared with standard MI care (San Roman et al., 2015).

This is the first-in-man study on myocardial adipose grafting and we should be restrained in interpreting the results, but findings suggest an improvement in necrosis area in AGTP-treated patients during early follow-up. Future studies are needed to determine whether this innovation translates to superior cardiac function with longer follow-up. This study provides evidence that use of an autologous vascular adipose graft may be a safe alternative in patients with a chronic myocardial scar. A Phase II—III multicenter, prospective, randomized clinical trial is now being set-up to confirm efficacy of the AGTP intervention.

Fig. 4. Selected patient case: short-axis delayed enhanced images show the healthy (black) and infarcted myocardium (white) before and after AGTP; 4-chamber view shows patient’s volumes before and after AGTP. Arrows point out the attached adipose graft position in the treated patient. ECG shows a Q wave in leads III and aVF at baseline that is not present at follow-up ECGs.

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Authors’ Contributions

Antoni Bayes-Genis: Study concept and design, drafting of the manuscript, critical revision of the manuscript for important intellectual content, recruitment, and final approval of the version to be published.

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Maria-Luisa Cámara: Acquisition of data, recruitment and treatment, final approval of the version to be published.

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Josep Lupón: Acquisition of data, analysis and interpretation of data, statistical analysis, final approval of the version to be published.

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