Omentum support for cardiac regeneration in ischaemic cardiomyopathy models: a systematic scoping review

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Abstract

OBJECTIVES: Preclinical in vivo studies using omental tissue as a biomaterial for myocardial regeneration are promising and have not previously been collated. We aimed to evaluate the effects of the omentum as a support for bioengineered tissue therapy for cardiac regeneration in vivo.

METHODS: A systematic scoping review was performed. Only English-language studies that used bioengineered cardio-regenerative tissue, omentum and ischaemic cardiomyopathy in vivo models were included.
RESULTS: We initially screened 1926 studies of which 17 were included in the final qualitative analysis. Among these, 11 were methodologically comparable and 6 were non-comparable. The use of the omentum improved the engraftment of bioengineered tissue by improving cell retention and reducing infarct size. Vascularization was also improved by the induction of angiogenesis in the transplanted tissue. Omentum-supported bioengineered grafts were associated with enhanced host reverse remodelling and improved haemodynamic measurements.

CONCLUSIONS: The omentum is a promising support for myocardial regenerative bioengineering in vivo. Future studies would benefit from more homogenous methodologies and reporting of outcomes to allow for direct comparison.

Keywords: Omentum • Cardiac regeneration • Omental flap • Omentopexy • In vivo models • Vascularization

INTRODUCTION

Ischaemic heart disease remains the leading global cause of mortality and is rising in prevalence with population growth, ageing effects and shifting epidemiological trends [1, 2]. For end-stage heart failure patients, transplantation and mechanical circulatory assistance devices are 2 of the limited options to restore a better quality of life [3]. Donor shortage and the limited regenerative potential of myocardium have led to the recent development of numerous cell-based therapies for cardiac tissue engineering [2, 4–10].

The omentum has been used as a support for cardiac bioengineering to overcome some of the challenges in myocardial regeneration, such as poor vascularization and engraftment of bioengineered tissue [2, 11–14]. It has regenerative properties that have been exploited in surgical techniques, such as omental transposition, where the omentum is extended or wrapped around another tissue to promote healing, including the heart in cardio-omentopexy [15]. It is thought that these regenerative capabilities are linked to the presence of angiogenic factors, including vascular endothelial growth factor, basic fibroblast growth factor and an abundance of progenitor cells [16]. Its abundance of collagens, glycosaminoglycans and adhesive proteins is hypothesized to support the morphological, physiological and biochemical properties of bioengineered cardiac tissues to be more akin to native myocardium [17, 18].

Rapid preclinical progress with omental-cardiac support has not previously been collated; therefore, we conducted a systematic scoping review [19]. The primary aim was to determine what is currently known about the effectiveness of the omentum as a biomaterial in regenerative strategies for in vivo models of myocardial infarction (MI). The outcomes of interest that will be explored include: (i) engraftment of bioengineered cardiac tissues; (ii) tissue vascularization; (iii) reduction in pathological cardiac remodelling and (iv) functional cardiac and haemodynamic improvement. Gaps in the literature will be identified, and future research directions indicated.

MATERIALS AND METHODS

Eligibility criteria for initial database search

Any English-language study in a peer-reviewed journal reporting on the use of the omentum in bioengineered cardiac tissue was considered in the original database search. Only original scientific articles were included. Conference abstracts, letters, case reports, editorials without a full text and reviews were excluded.

Search strategy and screening process

The databases Embase, Medline, PubMed, Scopus and Web of Science were searched by 1 reviewer (H.W.) from inception until 6 August 2019. The search terms used were: (omentum OR oment*) AND (cardiac OR heart).

Identified studies were imported into bibliographic management software, Endnote X9 (Clarivate Analytics, Philadelphia, PA, USA), and duplicated studies were deleted. One reviewer (H.W.) screened the title and abstract of each citation. For each eligible citation, the full text was obtained and independently screened by 2 reviewers (H.W. and C.D.R.) for the assessment of full-text inclusion. Reference lists of included articles were also searched for additional studies not captured by the original search. Disagreements were resolved by discussion. The criteria for full-text inclusion were as follows:

- The use of the greater omentum as a biomaterial, flap or in omentopexy;
- An ischaemic cardiomyopathy model (animal and/or human tissue);
- The implantation of biomaterials, including non-cardiac cell types, onto the infarcted heart; and
- Implantation efficacy expressed in terms of morphological, biochemical or physiological integration with host tissue.

Data extraction

Extraction tables were used to standardize the collection of data from the included studies (Tables 1–6). One reviewer (H.W.) extracted the data initially, and the second reviewer verified the data (C.D.R).

RESULTS

Study selection and characteristics of studies

The process of study selection into the review is represented in Fig. 1, a PRISMA flowchart [37]. A total of 17 studies met the inclusion criteria. The 11 comparable studies using a pedicled omental flap technique underwent comparable data extraction (Tables 1–4). Those using non-comparable methodologies [31–33] or control groups [34–36] were separated out and are displayed in Tables 5 and 6, respectively.

Of the 17 selected studies, 6 used a rat MI model [23, 25, 29, 30, 33, 35], 7 used a porcine MI model [20–22, 24, 28, 32, 34], 3 used a rabbit MI model [26, 27, 36] and 1 used a sheep MI model [31].

ABBREVIATIONS

| Abbreviation | Description |
|--------------|-------------|
| LVEF | Left ventricular ejection fraction |
| MI | Myocardial infarction |
Bioengineering cardiac tissue involved a variety of approaches, including the use of skeletal myoblast cells [20, 24, 25, 31, 34], cells derived from the omentum itself [31, 32], scaffolds for factor delivery [26–28, 33], atrial tissue [29], hepatic tissue [35], uterine cells derived from the omentum itself [31, 32], scaffolds for factor delivery including the use of skeletal myoblast cells [20, 24, 25, 31, 34], and others. Studies examining changes in infarct size, 2 reported a decrease after 4 weeks or less after treatment. Effects of omentum support on bioengineered tissue engraftment

Measures of engraftment were reported in 9 methodologically comparable studies (those using a pedicled omental flap to support bioengineered tissue) using various metrics at various time points (Table 2). They were tested between the time period of 7 days to 3 months across these studies, with most reporting effects in 4 weeks or less after treatment.

Transplanted cell retention. In 6 methodologically comparable studies, cell survival was evaluated following transplantation (Table 2) [22, 23, 25, 29, 30, 34]. Only one study [23] found that the omentum had no effects in promoting cell survival. All remaining studies reported greater cell survival and/or decreased apoptosis for omentum-supported treatment compared to bioengineered tissue applied without supportive omentopexy (Table 2).

Cell markers. From all of the 17 selected studies, the most common report of a structural integration marker was the presence of connexin-43, a gap junction protein, critical for propagation of the depolarization impulse between transplanted cells and host myocardium [30, 32, 33, 36]. In 2 of these studies, a higher expression of connexin-43 was observed in omentum-supported groups compared to treatment without omentum [30, 32]. Only one paper reported on the presence of troponin-T and actinin staining to corroborate microscopic observations of distinctive bundled cardiac muscle structures in transplanted tissue [33]. However, this was not compared to their frequency in control groups.

Structural integration. Two of 17 studies described fibre organization of the bioengineered tissue [22, 33]. Omentum-supported neonatal cardiac cells in an alginate scaffold and cardiomyocyte cell sheets transplanted onto ischaemic myocardium both exhibited desirable attributes, such as striation and elongation [22, 33]. Kawamura et al. [22] reported that the omentum contributed to the further maturation of induced pluripotent stem cell-derived cardiomyocytes, characterized by larger cells with well-aligned and organized sarcomere structures with positive staining for myosin heavy chain and myosin light chain-2 in the transplanted area at 2 months after omentum-supported treatment.

Table 1: Studies which used a pedicled omental flap as support for bioengineered tissue to regenerate the myocardium

| First author | Year | In vivo model | Coronary artery for MI | Intervention interval after MI | N per group | Bioengineered cardiac tissue | Mode of tissue delivery |
|--------------|------|---------------|------------------------|-------------------------------|-------------|----------------------------|--------------------------|
| Kainuma et al. [20] | 2015 | Pig           | LCA                    | 2 weeks                       | 11          | Skeletal myoblast cell sheet | Transplantation onto MI/peri-infarct area |
| Kanamori et al. [21] | 2006 | Minipig       | OM1 + 2 Distal D1      | 1 h                           | 5           | Autologous bone marrow-derived mononuclear cells | Injection into MI/peri-infarct area |
| Kawamura et al. [22] | 2017 | Pig           | LAD                    | 1 month                       | 7           | Human iPSC cardiomyocyte cell sheets | Transplantation onto MI area |
| Lilyanna et al. [23] | 2013 | Rat           | LAD                    | 2 weeks                       | 11          | Fibrin graft containing cord-lining mesenchymal stem cells | Transplantation onto MI area |
| Shudo et al. [24] | 2011 | Minipig       | LAD                    | 4 weeks                       | 6           | Cell sheets consisting of skeletal myoblast cells | Transplantation onto MI/peri-infarct area |
| Suzuki et al. [25] | 2009 | Rat           | LAD                    | At initial procedure          | 10          | Myocardial cell sheets       | Transplantation onto MI area |
| Takaba et al. [26] | 2006 | Rabbit        | Cx                     | 4 weeks                       | 8           | Gelatine hydrogel sheet with bFGF applied | Transplantation onto MI area |
| Ueyama et al. [27] | 2004 | Rabbit        | Cx                     | At initial procedure          | 10          | Gelatine hydrogel sheet with bFGF applied | Transplantation onto MI area |
| Yajima et al. [28] | 2018 | Pig           | LAD                    | 4 weeks                       | 6           | Gelatine compressed sponge immersed in ONO-13301ST (slow-releasing synthetic prostacyclin agonist) | Transplantation onto MI area |
| Zhang et al. [29] | 2011 | Rat           | LCA                    | 3 weeks                       | 17          | Autologous tissue patch from left atrial appendage | Transplantation onto MI area |
| Zhou et al. [30] | 2010 | Rat           | LCA                    | 8 weeks                       | 16          | Cell patch of poly lactic acid-co-glycolic acid polymer seeded with mesenchymal stem cells | Transplantation onto MI area |

*aDefined as the treatment group in which both the bioengineered cardiac tissue and greater omentum were applied.

bFGF: basic fibroblast growth factor; Cx: circumflex coronary artery; D1: first diagonal artery; iPSC: induced pluripotent stem cell; LAD: left anterior descending coronary artery; LCA: left coronary artery; MI: myocardial infarction; OM1 + 2: obtuse marginal coronary artery 1 and 2.
omentum-supported treatment compared to the control group not using the omentum [24, 27] and 2 reported no difference [23, 29]. Omentum support was shown to increase myocardial wall thickness in 2 methodologically comparable studies [20, 26] and one that did not use a pedicled omental flap [33], although 2 studies showed no significant difference with omental flap support [27, 29]. All studies that examined percentage collagen in the myocardium demonstrated collagen attenuation, leading to decreased cardiac fibrosis, in omentum-supported treatment [20, 30, 35].

Overall results showed that omentum support had a favourable effect on the engraftment of cells for bioengineering strategies to regenerate the heart after MI.

Effects of omentum support on vascularization

**Blood vessel formation.** Direct blood vessel communication between the bioengineered tissue and omentum was observed in 4 methodologically comparable studies as contributing to a network of vessels that would Anastomose with the host myocardium (Table 3 and Fig. 2) [20, 21, 26, 27]. Whilst most comparable studies demonstrated that support with a pedicled omental flap led to greater vessel density in the transplantation area, there were variable reports of whether arteriolar or capillary density was increased (Table 3).

Of all 17 selected studies, 7 reported that arteriolar density was improved [21, 23, 25–28, 35], whilst 5 reported that capillary density had improved [22, 25, 30, 31, 35] and 2 did not specify vessel diameter [20, 33]. No negative relationship between blood vessel density and use of omentum support was reported in any study.

**Angiogenic markers.** Of all 17 selected studies, many corroborated the observation of increased vascularization with the up-regulated expression of genes related to angiogenesis [20, 22, 24, 25, 28–30, 33, 35]. The most commonly reported up-regulated gene in omentum-supported tissue was vascular endothelial growth factor [20, 22, 24, 25, 30, 35]. There were also reports of increased basic fibroblast growth factor [22, 35] and smooth muscle actin [28, 33].

**Blood flow.** Taken together, these results suggested that omentum support conveyed a proangiogenic effect. However, despite the potential for this to lead to increased myocardial blood flow or coronary flow reserve, only 2 studies in total reported that treatment supported by the omentum was superior to that of other treatment groups for blood flow [20, 26]. Two studies reported that omentum support made no significant difference to observed blood flow [21, 28].

Effects of omentum-supported bioengineered tissue on cardiac remodelling and function

**Remodelling.** Eight studies reported that bioengineered tissue supported with a pedicled omental flap decreased cardiac remodelling (Table 4). Seven studies reported a decrease in left
| First author                  | Cell retention                                      | Fibre organization and contacts formed | Infarct size, scar and wall changes |
|------------------------------|-----------------------------------------------------|----------------------------------------|-----------------------------------|
| Kainuma et al. [20]          | Engrafted area remaining with time                  |                                        |                                   |
|                              | Day 7 = 0.3 mm²                                     |                                        |                                   |
|                              | Day 28 = 0.15 mm²                                  |                                        |                                   |
|                              | Day 7 = 0.07 mm²                                   |                                        |                                   |
|                              | Day 28 = 0.05 mm²                                  |                                        |                                   |
| Key findings                 | ~3–4 × increased area of grafted cells remained in situ with omentum supporta | Well-organized sarcomere structure in cells with omentum support (not compared to control) | Collagen content 8% LV wall thickness 912 µm Myocyte size 16 µm Myocyte size 20 µm |
| Kawamura et al. [22]         | Cell % survival rate                               |                                        |                                   |
|                              | 1 month = 90%                                      |                                        |                                   |
|                              | 3 months = 58%                                     |                                        |                                   |
|                              | 1 month = 61%                                      |                                        |                                   |
|                              | 3 months = 24%                                     |                                        |                                   |
| Key findings                 | Improved grafted cell survival with omentum supporta |                                        |                                   |
| Lilyanna et al. [23]         | Bioluminescence photon emission flux of labelled live donor cells (photons/s) | Myosin heavy chain/myosin light chain-2 positive (striated filaments) | Scar size (LV cross sectional area % containing fibrosis) 34.7% 35.7% |
|                              | Day 1 = 6.5 × 10⁸                                   | Present                                |                                   |
|                              | Day 14 = 1.5 × 10⁸                                  | Not reported                           |                                   |
| Key findings                 | Donor cell attrition rate in vivo over time comparable with or without omentum support |                                        |                                   |
| Shudo et al. [24]            | Cardiomyocyte survival 46%                         |                                        |                                   |
|                              | Cell sheet thickness 120 µm                         |                                        |                                   |
|                              | 31%                                                |                                        |                                   |
|                              | 70 µm                                              |                                        |                                   |
| Key findings                 | Improved graft survival with omentum support       |                                        |                                   |
| Suzuki et al. [25]           | Cardiomyocyte survival 46%                         |                                        |                                   |
| Takaba et al. [26]           | Dynamic % wall thickening of infarct region 49% 41% |                                        |                                   |
| Key findings                 | % fractional wall thickening (assessed by cine MRI for quantitative wall motion) increased with omentum support |                                        |                                   |
| Ueyama et al. [27]           | Atrial tissue patch graft presence after 4 weeks   |                                        |                                   |
|                              | In situ                                            |                                        |                                   |
|                              | Scar thickness                                     |                                        |                                   |
|                              | ~0.4 mm (ns)                                       |                                        |                                   |
|                              | ~0.35 mm (ns)                                      |                                        |                                   |
| Key findings                 | Reduced infarct size, dilatation and scar. No significant difference in wall thickness |                                        |                                   |
| Zhang et al. [29]            | Infarct size 10%                                  |                                        |                                   |
|                              | LV circumference 48 mm                            |                                        |                                   |
|                              | Scar circumference 16 mm                           |                                        |                                   |
|                              | Infarct area wall thickness 2.5 mm (ns)            |                                        |                                   |
|                              | 2.0 mm (ns)                                        |                                        |                                   |
| Key findings                 |                                                      |                                        |                                   |

*Continued*
ventricular end-diastolic diameter in the range of 2–25%, and 5 studies reported a decrease in left ventricular end-systolic diameter in the range of 10–27% (Table 4). For reverse remodelling, the study that reported the most beneficial effect did not involve a pedicled omental flap, but rather pre-vascularization of a cardiac patch on the omentum, supplemented with angiogenic factors, before transplanting the patch without omentopexy onto the heart [33]. Nevertheless, combining bioengineered tissue with an omental flap favoured reverse remodelling, especially at 4 weeks or later after intervention (Table 4).

**Function.** The most common measure of functional improvement reported was the left ventricular ejection fraction (LVEF). Omentum-supported bioengineered tissue improved the LVEF by up to 82% as a relative increase on absolute values compared to controls receiving bioengineered tissue alone (Table 4). Conversely, omentopexy alone without a bioengineered tissue was not enough to significantly improve LVEF [25, 29]. Results for fractional shortening and fractional area change were reported with less frequency than LVEF with only 3 studies reporting a significant increase in fractional shortening [26, 29, 30] and 1 study reporting an increase in fractional area change [27] with omentum support (Table 4).

**DISCUSSION**

This is the first review that systematically evaluates the effects of omentum support for bioengineering of cardiac tissues in MI models *in vivo*. Although all the included studies demonstrated that the omentum conferred a benefit in at least one of the outcomes assessed (engraftment, vascularization, remodelling, function), only a few studies reported on all outcomes. Furthermore, a few did not contain optimal control groups. This makes it difficult to draw conclusions of how effective the omentum is compared to controls or other bioengineering strategies. Our results highlight the variability of methodologies and results between studies (such as the treatment modality combined with the omentum, the model of MI and the outcome measures). This limits the extent to which the benefit of the omentum can be compared across studies.

The synergistic proangiogenic potential of omentum-supported bioengineered tissue was instrumental in most studies to promoting greater vascularization than bioengineered treatment or omentopexy alone. The development of a microvasculature between the coronary and gastroepiploic circulation was reported (Fig. 2) [20, 21, 26, 28]. The up-regulation of several angiogenic genes and proteins (e.g. vascular endothelial growth factor and smooth muscle actin) suggested that angiogenesis and vessel maturation are supported by the omentum (Table 3). However, most studies demonstrated that enhanced vascularization of the bioengineered tissue did not ultimately correlate with increased myocardial blood flow [20, 21, 28, 34]. Therefore, additional studies are needed to make progress from these results before they can be translated into clinical trials.

As shown in Table 4, bioengineered tissues with omentum support reported positive effects on cardiac function at 4 weeks in 6 studies. Suzuki *et al.* [25] reported an improvement at 1 week, and Kawamura *et al.* [22] reported an improvement at 3 months. All studies reporting a significant positive effect on function (Table 4) also reported enhanced vascularization (Table 3). Five studies reported both improved engraftment and cardiac function (Tables 2 and 4). Altogether, this suggests that both vascularization and engraftment are required for a cardiac functional improvement. Furthermore, 2 studies [25, 29] showed that the omentum by itself did not significantly improve cardiac function. Despite promising functional results, future studies would benefit from observations of long-term outcomes as some measurements, such as LVEF, have limited prognostic power in predicting clinical benefit across long time horizons.
| First author | Blood vessel character | Comparison group: bioengineered tissue no omentum support or omentopexy alone | Blood vessel dynamics | Comparison group: bioengineered tissue no omentum support or omentopexy alone | Up-regulated vascular markers in omentum-supported tissue |
|--------------|------------------------|-----------------------------------------------------------------|------------------------|----------------------------------------------------------------|----------------------------------------------------------|
| Kainuma et al. [20] | Total CD31+ endothelial cells (mature and immature vessels) | ~275 cells/mm² | ~225 μm | VEGF (endothelial cells) | PDGF-β (pericytes) |
|               | Functionally mature vessels (CD31+/Lecithin+) | ~375 cells/mm² | 2nd–4th branch vessel diameter | Ang-1 (endothelial cells) | Ang-2 (angioblasts) |
|               | Structurally mature vessels (CD31+/SMA+) | ~225 cells/mm² | No difference | Tie-2 (angioblasts) | VE-cadherin (adult endothelial cells) |
|               | ~120 cells/mm² | ~30 cells/mm² | Resistance vessels (3rd–4th order) | PECAM (CD31) (endothelial cells) | |
|               | % Maturation (structurally mature vessels/total) | ~31% | ~2-3× more vessels | | |
|               | Gastroepiploic-coronary anastomoses | Present | ~12% | Acetylcholine challenge (resistance vessel diameter dilation) | | |
| Kanamori et al. [21] | Arteriole (>50 μm) density | 27/mm² | 28% (3rd order vessels) | VEGF (endothelial cells) | |
|               | Capillaries (<50 μm) density | 18/mm² | 32% (4th order vessels) | | |
|               | Gastroepiploic-coronary anastomotic tight junctions | 109/mm² (ns) | 31% (3rd order vessels) | | |
| Kawamura et al. [22] | Capillary density | 111 units/mm² | 120/mm² | | Up-regulation of multiple vascular molecular markers suggesting increased vascular cellularity with omentum support |
| Lilyanna et al. [23] | Structural blood vessels | 6/hpf (400×) | 3/hpf (400×) | | | |
| Shudo et al. [24] | Capillary density | 125/mm² | | | | |

Continued
| First author | Blood vessel character | Comparison group: bioengineered tissue no omentum support or omentopexy alone | Omentum-supported bioengineered tissue | Blood vessel dynamics | Comparison group: bioengineered tissue no omentum support or omentopexy alone | Up-regulated vascular markers in omentum-supported tissue |
|--------------|------------------------|--------------------------------------------------------------------------------|----------------------------------------|----------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------|
| Suzuki et al. [25] | Small vessels | VEGF (endothelial cells) | VWF (endothelial cells) | Up-regulation of markers suggesting increased endothelial cells |
| Key findings | Increased small vessels observed (anti-vWF antibody immunolabelled vessels) with omentum supporta | Regional MBF 2.8 ml/min/g | 2.3 ml/min/g | Regional MBF drop on clamping gastroepiploic artery pedicle 2.8–1.9 ml/min/g | No comparison data |
| Takaba et al. [26] | Arteriole (>50 μm) density | 31 vessels/mm² | Gastroepiploic-coronary anastomoses via omentum-supported tissue | Present | No comparison data |
| Key findings | Increased arterioles (anti-SMA antibody immunolabelled arterioles) with omentum support | Increased arterioles (anti-SMA antibody immunolabelled arterioles) with omentum support | Regional MBF | Increased arterioles (anti-SMA antibody immunolabelled arterioles) with omentum support |
| Ueyama et al. [27] | Arteriole (20–100 μm) density | 23/mm² | 14/mm² | Subjects with LV collateral vessels on angiography via gastroepiploic artery pedicle 7/7 (2/7)b |
| Key findings | Increased arterioles (anti-SMA antibody immunolabelled arterioles) with omentum support | Increased arterioles (anti-SMA antibody immunolabelled arterioles) with omentum support |
| Yajima et al. [28] | Arteriole (CD31+/SMA+) density | 31/mm² | Capillary (CD31+) density | ~98/mm² (ns) | Vessels >100 μm diameter | ~1.5/mm² (ns) | ~1.2/mm² (ns) |
| Key findings | Increased arteriole (CD31+ and SMA+ vessels) density and no difference for capillaries (CD31+ vessels) or >100 μm diameter vessels in peri-infarct area with omentum supporta | Increased arteriole (CD31+ and SMA+ vessels) density and no difference for capillaries (CD31+ vessels) or >100 μm diameter vessels in peri-infarct area with omentum supporta |
| Zhang et al. [29] | Capillary (VEGF+) density | ~48/0.2 mm² (ns) | ~28/0.2 mm² (ns) | VEGF (endothelial cells) (ns) |
| Key findings | No difference in capillary (VEGF+ vessels) density with omentum support versus bioengineered tissue alonea | No difference in capillary (VEGF+ vessels) density with omentum support versus bioengineered tissue alonea |
| Zhou et al. [30] | Microvessel (vWF+) density | 226/mm² | 109/mm² | VEGF (endothelial cells) |
| Key findings | Increased vessel (anti-vWF antibody immunolabelled microvessels) density with omentum support | Increased vessel (anti-vWF antibody immunolabelled microvessels) density with omentum support |

aNumerical data extrapolated from graphical figure.

bComparison to bioengineered tissue without omentum support is not applicable for this assay as no connection to gastroepiploic circulation is possible in this group. Therefore control group result is for omentopexy alone (no bioengineered tissue).

dIL is DiI18 (1,1'-dioctadecyl-3,3',3'-tetramethylindocarbocyanine perchlorate) fluorescent dye. Ang-1: angiopoietin 1; bFGF: basic fibroblast growth factor; CFR: coronary flow reserve; Cx: circumflex coronary artery; LV: left ventricle; MBF: myocardial blood flow; ns: result not statistically significant; PDGF-b: platelet-derived growth factor-β; PECAM: platelet endothelial cell adhesion molecule; SMA: smooth muscle actin; VEGF: vascular endothelial growth factor; vWF: von Willebrand factor.

REVIEW
**Limitations**

Limitations of this review include those inherent to the scoping review methodology, namely that other relevant studies may not have been included. Aside from those not in English, there remain innovative *in vitro* studies utilizing the omentum for bioengineered cardiac tissue that fell outside the scope of this review because they were not tested *in vivo*. Most studies captured by our scoping review used a pedicled omental flap, which is feasible in human surgery. This is perhaps why it featured so prominently and may lend itself to a smooth translation from the laboratory into clinical practice. However, only 17 publications out of 1926 were admissible for the lack of translation of *in vitro* work into *in vivo* experiments, which highlights a gap between scientists and clinicians. This should be addressed in all future studies to facilitate translating preclinical *in vivo* studies to human trials.

The tendency towards positive results from the studies found in this review may also present a publication bias. No studies in this review reported a detrimental effect and only a few reported no overall difference as a result of omentum support. This was despite the cardiac and diaphragmatic impairment that an omentopexy might cause in animal models. The results may also present attrition bias whereby animals that died as the result of the initial grafting procedure were not analysed. Furthermore, preclinical studies that pioneer new techniques are susceptible to scientific design weaknesses such as operator skill variability, tweaking of methods during experiments, non-randomization of animal subjects, small sample sizes and non-blinding of researchers [38]. Future *in vivo* experiments should explicitly address all of these points, adhering to an established experimental planning guideline, uploading protocols to un-editable repositories before work begins and including more systematic reporting on cardiac and respiratory functional outcomes beyond the LVEF.

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### Table 4: Cardiac functional outcomes of bioengineered tissue with omentum support compared to bioengineered tissue without omentum support

| First author            | LVEDD % decrease | LVESD % decrease | LVEF % increase | FS % increase | FAC % increase | Measurement interval after treatment |
|-------------------------|------------------|------------------|-----------------|--------------|---------------|--------------------------------------|
| Kainuma et al. [20]     | 10% (ns)b        | 13% (ns)b        | 12% (ns)b       | 24%c         |               | 2 weeks                              |
| Kawamura et al. [22]    |                  |                  |                 |              |               | 4 weeks                              |
| Lilyanna et al. [23]    |                  |                  |                 |              |               | 1 month                              |
| Shudo et al. [24]       | 24% (ns)b        | 36%b             | 15% (ns)        | 15% (ns)     | 6% (ns)       | 4 weeks                              |
| Suzuki et al. [25]      | 0% (ns)b         | 27%b             | 26%b            | 22%b         |               | 8 weeks                              |
| Takaba et al. [26]      | -3% (ns)b        | 82%              | 5% (ns)b        | 36%          |               | 4 weeks                              |
| Ueyama et al. [27]      | 26%b             |                  | 26%b            | 81%          |               | 8 weeks                              |
| Yajima et al. [28]      | 5% (ns)          | 14% (ns)         | 34% (ns)        |              |               | 2 weeks                              |
| Zhang et al. [29]       | 8%               | 10%              | 10%             | 6.3%         |               | 4 weeks                              |
| Zhou et al. [30]        | 13%              | 12%              | 13%             | 11%          |               | 4 weeks                              |

Data expressed as % decrease or % increase (whichever is the desirable outcome) between the absolute values for the omentum-supported and non-omentum-supported groups.

Numerical data extrapolated from graphical figure.

FAC: fractional area change; FS: fractional shortening; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; ns: result not statistically significant.

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![Diagram](image-url)  
Figure 2: Collateral blood vessel formation between the Cx and the GEA in omentum-supported bioengineered tissue applied to the heart in a rabbit model of Cx infarction.  
(A) The whole specimen (scale bar = 10 mm).  
(B) Collateral formation between occluded Cx and GEA (scale bar = 1 mm).  
(C) Scanning electron micrograph of collaterals between occluded Cx and GEA. Reproduced with permission from [36]. Cx: circumflex coronary artery; GEA: gastroepiploic artery.
The omentum has also been used in non-cardiac tissues for the promotion of regeneration and superior bioengineering techniques. In particular, the pedicled omental flap has been used in vivo for spinal wound repair [39] and synthetic patch reconstruction of the anterior abdominal wall [40]. Hepatocytes on biodegradable scaffolds [41] and tracheal [42] tissue have also been shown to grow successfully on the omentum. The common mechanism behind the regenerative potential of the omentum is likely due to its numerous paracrine factors and immunological mediators promoting the optimal stem cell niche [43]. A deeper understanding of the mechanisms regulating non-cardiac tissue regeneration may lead to future innovative approaches in cardiac bioengineering.

**CONCLUSION**

The omentum is a promising tissue for cardiac bioengineering. It has demonstrated its ability to enhance transplanted cell engraftment, vascularization and host cardiac function. The mechanisms that confer functional cardiac benefit are not fully understood and require further experimental consideration. Future studies that examine these mechanisms and outcomes would benefit from a more homogenous approach to methodology that promotes a more detailed understanding of mechanistic processes and outcomes, which is important for clinical translation.

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Author contributions
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