European Journal of Cardio-Thoracic Surgery 58 (2020) 1118–1129
doi:10.1093/ejcts/ezaa205 Advance Access publication 18 August 2020

REVIEW

Cite this article as: Wang H, Roche CD, Gentile C. Omentum support for cardiac regeneration in ischaemic cardiomyopathy models: a systematic scoping review. Eur J Cardiothorac Surg 2020;58:1118–29.

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

Hogan Wang [a], Christopher D. Roche [a,b,c,d] and Carmine Gentile [a,c,*]

[a] Northern Clinical School of Medicine, University of Sydney, Kolling Institute, St Leonards, Sydney, NSW, Australia
[b] Department of Cardiothoracic Surgery, Royal North Shore Hospital, St Leonards, Sydney, NSW, Australia
[c] Department of Biomedical Engineering, Faculty of Engineering and IT, University of Technology Sydney (UTS), Ultimo, Sydney, NSW, Australia
[d] Department of Cardiothoracic Surgery, University Hospital of Wales, Cardiff, UK

* Corresponding author. Department of Biomedical Engineering, Faculty of Engineering and IT, University of Technology Sydney (UTS), Building 11, 81 Broadway, Ultimo, Sydney, NSW 2007, Australia. Tel: +61-2-95144502; e-mail: carmine.gentile@uts.edu.au (C. Gentile).

Received 2 February 2020; received in revised form 6 April 2020; accepted 9 May 2020

Key question

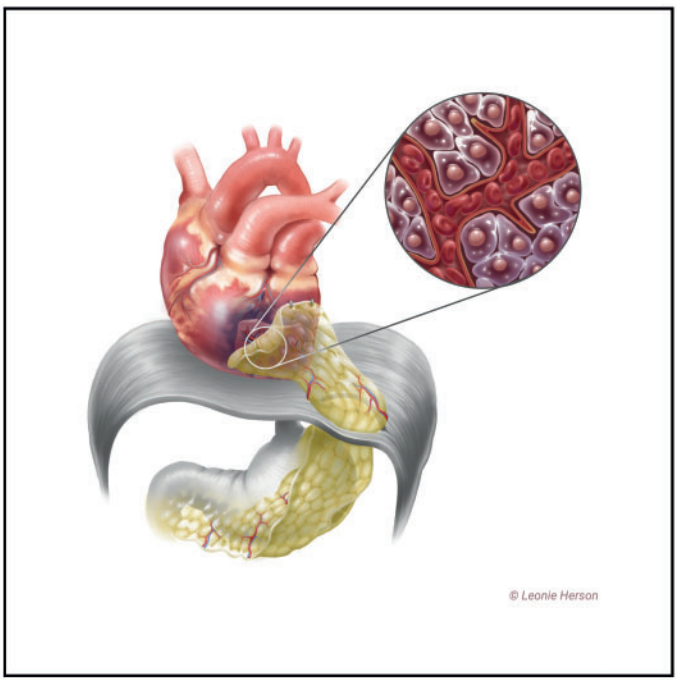
What are the effects of the omentum as a support for bioengineered tissue therapy for cardiac regeneration *in vivo*?

Key finding(s)

Omentum-supported bioengineering is associated with superior engraftment, vascularization and functional results *in vivo*.

Take-home message

Bioengineered cardiac tissue seems to benefit from omentum support *in vivo*. This promising tissue may boost progress in cardiac regeneration.



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

ABBREVIATIONS

LVEF	Left ventricular ejection fraction
MI	Myocardial infarction

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].

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[a]	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. Attached using fibrin glue
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 polylactic acid-co-glycolic acid polymer seeded with mesenchymal stem cells	Transplantation onto MI area

[a]Defined 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.

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 tissue [36] and stem cells [21–23, 30].

Fourteen studies transplanted the bioengineered tissue onto the MI and/or peri-infarct area whereas the remaining 3 [21, 31, 32] reported the injection of cells into the same areas.

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.

Infarct size. In the 4 methodologically comparable studies examining changes in infarct size, 2 reported a decrease after

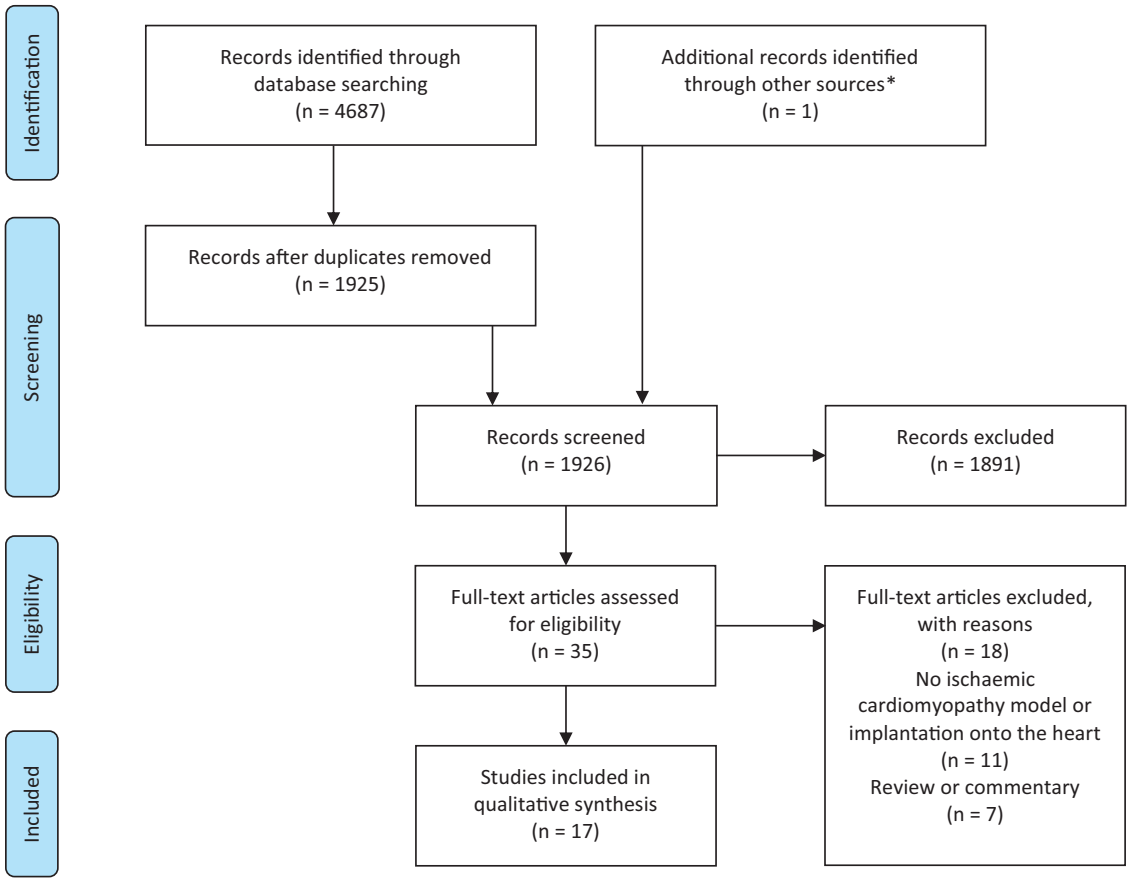


Figure 1: PRISMA flowchart of pathway for papers in the review. *Ueyama *et al.* [27] identified through reference list of an article accepted for full-text assessment.

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

Table 2: Measures of engraftment outcomes of bioengineered cardiac tissue with omentum

First author	Cell retention		Fibre organization and contacts formed		Infarct size, scar and wall changes	
	Omentum-supported bioengineered tissue	Comparison group: bioengineered tissue no omentum support	Omentum-supported bioengineered tissue	Comparison group: bioengineered tissue no omentum support	Omentum-supported bioengineered tissue	Comparison group: bioengineered tissue no omentum support
Kainuma *et al.* [20]	Engrafted area remaining with time Day 7 = 0.3 mm^2 Day 28 = 0.15 mm^2	Day 7 = 0.07 mm^2 Day 28 = 0.05 mm^2			Collagen content 8%	13%
					LV wall thickness 912 μm	688 μm
					Myocyte size 16 μm	20 μm
Key findings	∼3–4× increased area of grafted cells remained *in situ* with omentum support[a]				Scar collagen attenuation, less thick LV wall, reduced hypertrophy with omentum support	
Kawamura *et al.* [22]	Cell % survival rate 1 month = 90% 3 months = 58%	1 month = 61% 3 months = 24%	Myosin heavy chain/myosin light chain-2 positive (striated filaments) Present	Not reported		
Key findings	Improved grafted cell survival with omentum support[a]		Well-organized sarcomere structure in cells with omentum support (not compared to control)			
Lilyanna *et al.* [23]	Bioluminescence photon emission flux of labelled live donor cells (photons/s) Day 1 = 6.5×10^7 Day 14 = 1.5×10^5	Day 1 = 7.6×10^7 Day 14 = 6.8×10^5			Scar size (LV cross sectional area % containing fibrosis) 34.7%	35.7%
Key findings	Donor cell attrition rate *in vivo* over time comparable with or without omentum support				Minimal difference in scar with or without omentum support	
Shudo *et al.* [24]					Infarct area ∼6%	∼11%
Key findings					Infarct size (infarcted LV/total LV estimated by computer-based planimetry of Masson trichrome-staining) reduced with omentum support[a]	
Suzuki *et al.* [25]	Cardiomyocyte survival 46%	31%				
	Cell sheet thickness 120 μm	70 μm				
Key findings	Improved graft survival with omentum support					
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]					Infarct size 10%	16%
					LV circumference 48 mm	56 mm
					Scar circumference 16 mm	24 mm
					Infarct area wall thickness 2.5 mm (ns)	2.0 mm (ns)
Key findings					Reduced infarct size, dilatation and scar. No significant difference in wall thickness	
Zhang *et al.* [29]	Atrial tissue patch graft presence after 4 weeks *In situ*	Not seen			Scar thickness ∼0.4 mm (ns)	∼0.35 mm (ns)
					Infarct size ∼38% (ns)	∼39% (ns)

Continued

Table 2: Continued

First author	Cell retention		Fibre organization and contacts formed		Infarct size, scar and wall changes	
	Omentum-supported bioengineered tissue	Comparison group: bioengineered tissue no omentum support	Omentum-supported bioengineered tissue	Comparison group: bioengineered tissue no omentum support	Omentum-supported bioengineered tissue	Comparison group: bioengineered tissue no omentum support
Key findings	Troponin-stained graft survived with omentum support but did not without omentum support				No significant difference in scar thickness or infarct size with or without omentum support[a]	
Zhou *et al.* [30]	Quantification PCR of grafted cells[b] Week 1 = 14.1 units Week 4 = 2.6 units	 Week 1 = 3.8 units Week 4 = 1.2 units	Connective protein Cx-43 expression[c] 0.23 units	 0.19 units	Collagen (scar) density 16%	 26%
Key findings	Cell survival rate *in vivo* over time improved with omentum support		Higher levels of Cx-43 suggested enhanced structural coupling of transplanted cells to host myocardium. Sham group (baseline) level = 0.31; MI with no treatment group level = 0.11		Reduced % fibrillar collagen in the infarction zone (semiquantitatively measured by picrosirius red staining under polarized light microscopy)	

[a]Numerical data extrapolated from graphical figure.
[b]Units expressed as ratio of optical density under UV light compared to reference sample at the same time.
[c]Cx-43 protein expression determined by western blot. Units expressed as ratio to the level of β-actin which was run on all blots.
Cx-43: connexin-43; LV: left ventricle; MI: myocardial infarction; MRI: magnetic resonance imaging; ns: result not statistically significant; PCR: polymerase chain reaction; UV: ultra-violet.

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.

Table 3: Measures of vascularization outcomes of bioengineered cardiac tissue with omentum

First author	Blood vessel character		Blood vessel dynamics		Up-regulated vascular markers in omentum-supported tissue
	Omentum-supported bioengineered tissue	Comparison group: bioengineered tissue no omentum support or omentopexy alone	Omentum-supported bioengineered tissue	Comparison group: bioengineered tissue no omentum support or omentopexy alone	
Kainuma *et al.* [20]	*Total* CD31+ endothelial cells (mature and immature vessels) ~425 cells/mm^2	~275 cells/mm^2	1st branching order vessel diameter ~225 μm	~170 μm	VEGF (endothelial cells) PDGF-β (pericytes) Ang-1 (endothelial cells) Tie-2 (angioblasts) VE-cadherin (adult endothelial cells) PECAM (CD31) (endothelial cells)
	Functionally mature vessels (CD31+/Lecithin+) ~375 cells/mm^2	~225 cells/mm^2	2nd–4th branch vessel diameter No difference	No difference	
	Structurally mature vessels (CD31+/SMA+) ~120 cells/mm^2	~30 cells/mm^2	Resistance vessels (3rd–4th order) ~2–3× more vessels	~2–3× fewer vessels	
	% Maturation (structurally mature vessels/total) ~31%	~12%	Acetylcholine challenge (resistance vessel diameter dilation) 28% (3rd order vessels) 32% (4th order vessels)	18% (3rd order vessels) 21% (4th order vessels)	
	Gastroepiploic-coronary anastomoses Present	(Absent)[b]	Dobutamine challenge (resistance vessel diameter constriction) 31% (3rd order vessels) 34% (4th order vessels)	9% (3rd order vessels) 29% (4th order vessels)	
	Gastroepiploic-coronary anastomotic tight junctions Present	(Absent)[b]	Global CFR change (ratio pre:post-treatment) 1.3	0.9	
	Gastroepiploic-coronary anastomotic ink leakage Minimal	(Widespread)[b]	MBF (resting or stressed) No difference	No difference	
Key findings	1. Increase in total vascularity and mature vascularity peri-infarct at 28 days with omentum support[a] 2. Anastomoses formed between omental and coronary circulation only if bioengineered tissue omentum-supported		1. Greater number and responsiveness of resistance vessels (3rd–4th order in descending hierarchy of calibre) 2. Increase in global CFR change and no change in MBF pre- to post-treatment with omentum support[a]		Up-regulation of multiple vascular molecular markers suggesting increased vascular cellularity with omentum support
Kanamori *et al.* [21]	Arteriole (>50 μm) density 27/mm^2	18/mm^2	Regional MBF (infarct or non-infarct wall, resting or stressed) No difference	No difference	
	Capillaries (<50 μm) density 109/mm^2 (ns)	88/mm^2 (ns)	Regional MBF ratio infarct: non-infarct wall (resting or stressed) No difference	No difference	
	Gastroepiploic-coronary anastomoses via omentum-supported tissue Present	No comparison data			
Key findings	1. Arteriole density increased but no significant difference for capillaries (<50 μm) 2. Anastomoses formed between omental and coronary circulation via omentum-supported bioengineered tissue		No difference in regional MBF (assessed by spectrophotometry of coloured microsphere cardiac injection with femoral arterial blood reference sampling) with omentum support compared to bioengineered tissue without omentum support		
Kawamura *et al.* [22]	Capillary density 111 units/mm^2	51 units/mm^2			VEGF (endothelial cells) bFGF (fibroblasts/angiogenesis)
Key findings	Increased capillary density at the transplanted area (assessed by semiquantitative immunohistochemistry for vWF) with omentum support				Up-regulation of markers suggesting increased endothelial cells and angiogenesis with omentum support
Lilyanna *et al.* [23]	Functional blood vessels as % of LV scar area 18%	8%			
	Structural blood vessels 6/hpf (400×)	3/hpf (400×)			
Key findings	Increased vascularity with functional staining (infused DiI+ vessels[c]) and structural staining (Masson's trichrome) with omentum support				
Shudo *et al.* [24]	Capillary density 170/mm^2	125/mm^2			VEGF (endothelial cells) vWF (endothelial cells)
Key findings	Increased capillaries (anti-vWF antibody immunolabelled capillaries) with omentum support				Up-regulation of markers suggesting increased endothelial cells

Continued

Table 3: Continued

First author	Blood vessel character		Blood vessel dynamics		Up-regulated vascular markers in omentum-supported tissue
	Omentum-supported bioengineered tissue	Comparison group: bioengineered tissue no omentum support or omentopexy alone	Omentum-supported bioengineered tissue	Comparison group: bioengineered tissue no omentum support or omentopexy alone	
Suzuki *et al.* [25]	Small vessels				VEGF (endothelial cells)
	70/hpf	20/hpf			vWF (endothelial cells)
Key findings	Increased small vessels observed (anti-vWF antibody immunolabelled vessels) with omentum support[a]				Up-regulation of markers suggesting increased endothelial cells
Takaba *et al.* [26]	Arteriole (>50 μm) density		Regional MBF		
	31 vessels/mm^2	26 vessels/mm^2	2.8 ml/min/g	2.3 ml/min/g	
	Gastroepiploic-coronary anastomoses via omentum-supported tissue		Regional MBF drop on clamping gastroepiploic artery pedicle		
	Present	No comparison data	2.8–1.9 ml/min/g	No comparison data	
Key findings	1. Increased arterioles (anti-SMA antibody immunolabelled arterioles) with omentum support 2. Anastomoses formed between omental and coronary circulation via omentum-supported bioengineered tissue		1. Infarct regional MBF increased with omentum support 2. Clamping gastroepiploic pedicle for omentum-supported bioengineered tissue caused 32% drop in host infarct regional MBF		
Ueyama *et al.* [27]	Arteriole (20–100 μm) density		Subjects with LV collateral vessels on angiography via gastroepiploic artery pedicle		
	23/mm^2	14/mm^2	7/7	(2/7)[b]	
			Collateral vessel description		
			Rich	(Poor)[b]	
			Patent collateral vessel proportion (angiographic score)		
			0.8	(0.1)[b]	
Key findings	Increased arterioles (anti-SMA antibody immunolabelled arterioles) with omentum support		Dye injection into gastroepiploic pedicle at immediate post-mortem angiography showed favourable collateral vessel patency for omentum-supported bioengineered tissue compared to omentopexy alone		Up-regulation of markers suggesting increased endothelial cells
Yajima *et al.* [28]	Arteriole (CD31+/SMA+) density		Global MBF		CD31 (endothelial cells)
	31/mm^2	20/mm^2	∼1.3 (ns)	∼1.0 (ns)	SMA (smooth muscle cells)
	Capillary (CD31+) density		Territorial and regional MBF		VEGF (endothelial cells) (ns)
	∼98/mm^2 (ns)	∼90/mm^2 (ns)	No difference	No difference	bFGF (fibroblasts/ angiogenesis) (ns)
	Vessels >100 μm diameter		CFR proportional change on occlusion of Cx artery with gastroepiploic pedicle not occluded		
	∼1.5/mm^2 (ns)	∼1.2/mm^2 (ns)	∼1.0	(∼0.7)[b]	
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 support[a]		1. No significant difference in MBF with omentum support 2. On clamping the Cx coronary artery for subject animals with LAD infarcts there was no change in CFR with omentum-supported bioengineered tissue compared to a 30% drop in CFR with omentopexy alone without bioengineered tissue		Up-regulation of markers suggesting increased endothelial cells
Zhang *et al.* [29]	Capillary (VEGF+) density				VEGF (endothelial cells) (ns)
	∼48/0.2 mm^2 (ns)	∼28/0.2 mm^2 (ns)			
Key findings	No difference in capillary (VEGF+ vessels) density with omentum support versus bioengineered tissue alone[a]				No difference in up-regulation of VEGF
Zhou *et al.* [30]	Microvessel (vWF+) density				VEGF (endothelial cells)
	226/mm^2	109/mm^2			
Key findings	Increased vessel (anti-vWF antibody immunolabelled microvessels) density with omentum support				Up-regulation of VEGF suggesting increased endothelial cells

[a]Numerical data extrapolated from graphical figure.

[b]Comparison 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).

[c]DiI is $DiIC_{18}$ (1,1′-dioctadecyl-3,3,3′,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-β: platelet-derived growth factor-β; PECAM: platelet endothelial cell adhesion molecule; SMA: smooth muscle actin; VEGF: vascular endothelial growth factor; vWF: von Willebrand factor.

Table 4: Cardiac functional outcomes of bioengineered tissue with omentum support compared to bioengineered tissue without omentum support[a]

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]			2 weeks
	16%[b]	16%[b]	24%[b]			4 weeks
Kawamura *et al.* [22]			5% (ns)			1 month
			8% (ns)			2 months
	25%	26%	16%			3 months
Lilyanna *et al.* [23]			15% (ns)	15% (ns)	6% (ns)	4 weeks
Shudo *et al.* [24]	24% (ns)[b]	36%[b]	26%[b]			4 weeks
	25% (ns)[b]	27%[b]	22%[b]			8 weeks
Suzuki *et al.* [25]	0% (ns)[b]		3%[b]			1 week
	10% (ns)[b]		8%[b]			4 weeks
	12%[b]		18%[b]			8 weeks
Takaba *et al.* [26]	-3% (ns)[b]		82%	5% (ns)[b]		4 weeks
	2%			36%		8 weeks
Ueyama *et al.* [27]	26%[b]				26%[b]	2 weeks
	21%				41%	4 weeks
Yajima *et al.* [28]	5% (ns)	14% (ns)	34% (ns)			4 weeks
Zhang *et al.* [29]	8%	10%	10%	6.3%		4 weeks
Zhou *et al.* [30]	13%	12%	13%	11%		4 weeks

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

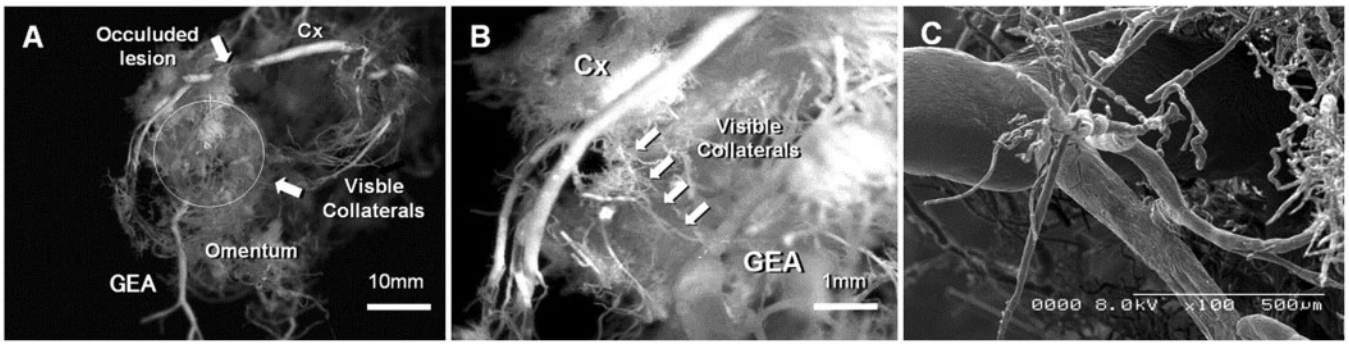


Figure 2: Collateral blood vessel formation between the Cx and the GEA in omentum-supported bioengineered tissue applied to the heart in a rabbit model of Cx infarction. (**A**) The whole specimen (scale bar = 10 mm). (**B**) Collateral formation between occluded Cx and GEA (scale bar = 1 mm). (**C**) Scanning electron micrograph of collaterals between occluded Cx and GEA. Reproduced with permission from [36]. Cx: circumflex coronary artery; GEA: gastroepiploic artery.

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.

Table 5: Studies that did not use an omental pedicled flap method

First author	Year	MI model *in vivo*	Coronary artery for MI	Intervention interval after MI	Subjects (*n*)/group	Bioengineered cardiac tissue	Method utilizing omentum	Mode of tissue delivery
Bourahla *et al.* [31]	2010	Sheep	LAD (distal) D2	3 weeks	10	Omental cells or skeletal myoblast cells	Isolation and expansion of autologous omental mesothelial cells	Injection into MI area
De Siena *et al.* [32]	2010	Pig	LAD	45 min	13	Human fat omentum-derived stromal cells	Isolation and expansion of human fat omentum-derived stromal cells	Injection into proximal MI border zone
Dvir *et al.* [33]	2009	Rat	LAD	1 week	11	Alginate-based cardiac patch containing neonatal cardiac cells and pro-survival and angiogenic factors (stromal cell-derived factor-1, IGF-1, VEGF)	Cardiac patch was vascularized on the omentum	Transplantation onto MI area

D2: second diagonal coronary artery; IGF-1: insulin-like growth factor 1; LAD: left anterior descending coronary artery; MI: myocardial infarction; VEGF: vascular endothelial growth factor.

Table 6: Studies that did not use a control group allowing for the comparison of bioengineered tissue with or without omentum support

Author	Year	MI model *in vivo*	Coronary artery for MI	Intervention interval after MI	Subjects (*n*)/group	Bioengineered cardiac tissue	Method utilizing omentum	Mode of tissue delivery
Kainuma *et al.* [34]	2018	Minipig	LAD (distal)	4 weeks	2	Skeletal myoblast cell sheet	Pedicled omentum flap	Transplantation onto MI area using transphrenic peritoneoscopy-assisted omentopexy
Shao *et al.* [35]	2008	Rat	LAD	30 min	11	Hepatic tissue resected from the left lobe of the liver	Pedicled omentum flap	Transplantation onto MI area
Taheri *et al.* [36]	2008	Rabbit	LAD	At initial procedure	6	Autologous graft using uterine segment	'Reinforcement' of myometrial patches	Transplantation onto MI area

LAD: left anterior descending coronary artery; MI: myocardial infarction.

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.

ACKNOWLEDGEMENTS

The authors thank Yulia Ulyannikova, Academic Liaison Librarian, University of Sydney for her guidance on the design of the literature search. They also thank Leonie Herson for her work in the design and generation of the central image.

Funding

C.D.R. was supported by a Sir John Loewenthal Scholarship 2019 (University of Sydney), the Le Gros Legacy Fund New Zealand

[PhD012019] and a Heart Research Australia Scholarship [PhD2019-02]. C.G. was supported by a University of Sydney Kick-Start Grant, University of Sydney Chancellor's Doctoral Incentive Programme Grant, a Sydney Medical School Foundation Cardiothoracic Surgery Research Grant, UTS Seed Funding and the Catholic Archdiocese of Sydney Grant for Adult Stem Cell Research (2019).

Conflict of interest: none declared.

Author contributions

Hogan Wang: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Validation; Visualization; Writing—original draft; Writing—review & editing. **Christopher D. Roche:** Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Validation; Writing—review & editing. **Carmine Gentile:** Conceptualization; Data curation; Funding acquisition; Methodology; Project administration; Supervision; Writing—review & editing.

Reviewer information

European Journal of Cardio-Thoracic Surgery thanks Claudia Heilmann, Luiz Felipe P. Moreira and Peter Zilla for their contribution to the peer review process of this article.

REFERENCES

[1] Naghavi M, Abajobir AA, Abbafati C, Abbas KM, Abd-Allah F, Abera SF *et al*. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1151–210.

[2] Roche CD, Brereton RJL, Ashton AW, Jackson C, Gentile C. Current challenges in three-dimensional bioprinting heart tissues for cardiac surgery. Eur J Cardiothorac Surg 2020;doi:10.1093/ejcts/ezaa093.

[3] Boilson BA, Raichlin E, Park SJ, Kushwaha SS. Device therapy and cardiac transplantation for end-stage heart failure. Curr Probl Cardiol 2010;35:8–64.

[4] Reis LA, Chiu LLY, Feric N, Fu L, Radisic M. Biomaterials in myocardial tissue engineering. J Tissue Eng Regen Med 2016;10:11–28.

[5] Duan B. State-of-the-art review of 3D bioprinting for cardiovascular tissue engineering. Ann Biomed Eng 2017;45:195–209.

[6] Sui R, Liao X, Zhou X, Tan Q. The current status of engineering myocardial tissue. Stem Cell Rev Rep 2011;7:172–80.

[7] Chachques JC, Lila N, Soler-Botija C, Martinez-Ramos C, Valles A, Autret G *et al*. Elastomeric cardiopatch scaffold for myocardial repair and ventricular support. Eur J Cardiothorac Surg 2020;57:545–55.

[8] Chachques JC, Trainini JC, Lago N, Cortes-Morichetti M, Schussler O, Carpentier A. Myocardial assistance by grafting a new bioartificial upgraded myocardium (MAGNUM trial): clinical feasibility study. Ann Thorac Surg 2008;85:901–8.

[9] Menasché P, Vanneaux V, Hagège A, Bel A, Cholley B, Parouchev A *et al*. Transplantation of human embryonic stem cell–derived cardiovascular progenitors for severe ischemic left ventricular dysfunction. J Am Coll Cardiol 2018;71:429–38.

[10] Menasché P, Vanneaux V, Hagège A, Bel A, Cholley B, Cacciapuoti I *et al*. Human embryonic stem cell-derived cardiac progenitors for severe heart failure treatment: first clinical case report. Eur Heart J 2015;36:2011–7.

[11] Tee R, Lokmic Z, Morrison WA, Dilley RJ. Strategies in cardiac tissue engineering. ANZ J Surg 2010;80:683–93.

[12] Noor N, Shapira A, Edri R, Gal I, Wertheim L, Dvir T. 3D printing of personalized thick and perfusable cardiac patches and hearts. Adv Sci 2019;6:1900344.

[13] Chachques JC, Pradas MM, Bayes-Genis A, Semino C. Creating the bioartificial myocardium for cardiac repair: challenges and clinical targets. Expert Rev Cardiovasc Ther 2013;11:1701–11.

[14] Vunjak-Novakovic G, Tandon N, Godier A, Maidhof R, Marsano A, Martens TP *et al*. Challenges in cardiac tissue engineering. Tissue Eng Part B Rev 2010;16:169–87.

[15] O'Shaughnessy L. Surgical treatment of cardiac ischaemia. Lancet 1937;229:185–94.

[16] Litbarg NO, Gudehithlu KP, Sethupathi P, Arruda JA, Dunea G, Singh AK. Activated omentum becomes rich in factors that promote healing and tissue regeneration. Cell Tissue Res 2007;328:487–97.

[17] Shevach M, Soffer-Tsur N, Fleischer S, Shapira A, Dvir T. Fabrication of omentum-based matrix for engineering vascularized cardiac tissues. Biofabrication 2014;6:024101.

[18] Soffer-Tsur N, Shevach M, Shapira A, Peer D, Dvir T. Optimizing the biofabrication process of omentum-based scaffolds for engineering autologous tissues. Biofabrication 2014;6:035023.

[19] Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc 2015;13:141–6.

[20] Kainuma S, Miyagawa S, Fukushima S, Pearson J, Chen YC, Saito A *et al*. Cell-sheet therapy with omentopexy promotes arteriogenesis and improves coronary circulation physiology in failing heart. Mol Ther 2015;23:374–86.

[21] Kanamori T, Watanabe G, Yasuda T, Nagamine H, Kamiya H, Koshida Y. Hybrid surgical angiogenesis: omentopexy can enhance myocardial angiogenesis induced by cell therapy. Ann Thorac Surg 2006;81:160–7.

[22] Kawamura M, Miyagawa S, Fukushima S, Saito A, Miki K, Funakoshi S *et al*. Enhanced therapeutic effects of human iPS cell derived-cardiomyocyte by combined cell-sheets with omental flap technique in porcine ischemic cardiomyopathy model. Sci Rep 2017;7:8824.

[23] Lilyanna S, Martinez EC, Vu TD, Ling LH, Gan SU, Tan AL *et al*. Cord lining-mesenchymal stem cells graft supplemented with an omental flap induces myocardial revascularization and ameliorates cardiac dysfunction in a rat model of chronic ischemic heart failure. Tissue Eng Part A 2013;19:1303–15.

[24] Shudo Y, Miyagawa S, Fukushima S, Saito A, Shimizu T, Okano T *et al*. Novel regenerative therapy using cell-sheet covered with omentum flap delivers a huge number of cells in a porcine myocardial infarction model. J Thorac Cardiovasc Surg 2011;142:1188–96.

[25] Suzuki R, Hattori F, Itabashi Y, Yoshioka M, Yuasa S, Manabe-Kawaguchi H *et al*. Omentopexy enhances graft function in myocardial cell sheet transplantation. Biochem Biophys Res Commun 2009;387:353–9.

[26] Takaba K, Jiang C, Nemoto S, Saji Y, Ikeda T, Urayama S *et al*. A combination of omental flap and growth factor therapy induces arteriogenesis and increases myocardial perfusion in chronic myocardial ischemia: evolving concept of biologic coronary artery bypass grafting. J Thorac Cardiovasc Surg 2006;132:891–9.

[27] Ueyama K, Bing G, Tabata Y, Ozeki M, Doi K, Nishimura K *et al*. Development of biologic coronary artery bypass grafting in a rabbit model: revival of a classic concept with modern biotechnology. J Thorac Cardiovasc Surg 2004;127:1608–15.

[28] Yajima S, Miyagawa S, Fukushima S, Sakai Y, Isohashi K, Watabe T *et al*. A prostacyclin agonist and an omental flap increased myocardial blood flow in a porcine chronic ischemia model. J Thorac Cardiovasc Surg 2018;156:229–41.e14.

[29] Zhang C, Hou J, Zheng S, Zheng Z, Hu S. Vascularized atrial tissue patch cardiomyoplasty with omentopexy improves cardiac performance after myocardial infarction. Ann Thorac Surg 2011;92:1435–42.

[30] Zhou Q, Zhou JY, Zheng Z, Zhang H, Hu SS. A novel vascularized patch enhances cell survival and modifies ventricular remodeling in a rat myocardial infarction model. J Thorac Cardiovasc Surg 2010;140:1388–96.e1–3.

[31] Bourahla B, Shafy A, Meilhac O, Elmadbouh I, Michel JB, Chachques JC. Mesothelial cells vs. skeletal myoblasts for myocardial infarction. Asian Cardiovasc Thorac Ann 2010;18:153–60.

[32] De Siena R, Balducci L, Blasi A, Montanaro MG, Saldarelli M, Saponaro V *et al*. Omentum-derived stromal cells improve myocardial regeneration in pig post-infarcted heart through a potent paracrine mechanism. Exp Cell Res 2010;316:1804–15.

[33] Dvir T, Kedem A, Ruvinov E, Levy O, Freeman I, Landa N *et al*. Prevascularization of cardiac patch on the omentum improves its therapeutic outcome. Proc Natl Acad Sci USA 2009;106:14990–5.

[34] Kainuma S, Nakajima K, Miyagawa S, Fukushima S, Saito A, Harada A *et al*. Novel regenerative therapy combined with transphrenic peritoneoscopy-assisted omentopexy. Interact CardioVasc Thorac Surg 2018;26:993–1001.

[35] Shao ZQ, Kawasuji M, Takaji K, Katayama Y, Matsukawa M. Therapeutic angiogenesis with autologous hepatic tissue implantation and omental wrapping. Circ J 2008;72:1894–9.
[36] Taheri SA, Yeh J, Batt RE, Fang Y, Ashraf H, Heffner R *et al*. Uterine myometrium as a cell patch as an alternative graft for transplantation to infarcted cardiac myocardium: a preliminary study. Int J Artif Organs 2008;31:62–7.
[37] Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
[38] Sade RM, Rylski B, Swain JA, Entwistle JWC, Ceppa DP, Blitzer D *et al*.; Members of the Cardiothoracic Ethics Forum who contributed to this work. Transatlantic editorial: institutional investigations of ethically flawed reports in cardiothoracic surgery journals. Eur J Cardiothorac Surg 2020;57:617–19.
[39] Sambri A, Gasbarrini A, Cialdella S, De Iaco P, Boriani S. Pedicled omental flaps in the treatment of complex spinal wounds after en bloc resection of spine tumors. J Plast Reconstr Aesthet Surg 2017;70:1267–71.
[40] Uchibori T, Takanari K, Hashizume R, Amoroso NJ, Kamei Y, Wagner WR. Use of a pedicled omental flap to reduce inflammation and vascularize an abdominal wall patch. J Surg Res 2017;212:77–85.
[41] Lee H, Cusick RA, Utsunomiya H, Ma PX, Langer R, Vacanti JP. Effect of implantation site on hepatocytes heterotopically transplanted on biodegradable polymer scaffolds. Tissue Eng 2003;9:1227–32.
[42] Li J, Xu P, Chen H, Yang Z, Zhang Q. Improvement of tracheal autograft survival with transplantation into the greater omentum. Ann Thorac Surg 1995;60:1592–6.
[43] Behfar A, Crespo-Diaz R, Terzic A, Gersh BJ. Cell therapy for cardiac repair—lessons from clinical trials. Nat Rev Cardiol 2014;11:232–46.