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O omento maior pode ser doador de células-tronco ao miocárdio isquêmico?

O omento maior pode ser doador de células-tronco ao miocárdio isquêmico?

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ABSTRACT

Introduction: Recent progress in the bioengineering of cardiac grafts offers a new therapeutic modality for the regeneration of cardiac tissue after myocardial infarction. CD34 is a marker that expresses all hematopoietic and endothelial precursor cells, and functions as a cell adhesion factor. The antibody corresponding to this marker is used in immunohistochemistry to evaluate the formation of new vessels and the presence of stem cells.

Objective: To evaluate the effectiveness of omentopexy in neovascularization and stem cells.

Methods: Review collecting information published on selected virtual platforms (SciELO – Scientific Electronic Library Online, Google Scholar, Pubmed and Scopus). The search began with descriptors related to the topic, identified through DeCS/MESH in the following: "myocardial ischemia; myocardial revascularization; omentopexy; immunohistochemistry; CD34; stem cells". They were read by title and summary, with an AND or OR search followed by the full reading of those most closely related to the topic. A total of 23 articles were included.

Results: The greater omentum has a remarkable clinical property in containing sites of tissue damage. It increases its tissue volume in response to foreign and inflammatory particles involving several immunomodulatory cells with progenitor cells, in a process called "omentum activation".

Conclusion: Cardio-omentopexy associated with mechanical abrasion and myocardial perforations proves to be efficient in inducing neovascularization. The greater omentum promotes stem cells - confirmed by CD34 -, demonstrating great potential as a future therapy to restore areas of ischemic myocardium.

KEYWORDS: Stem cell. Myocardial ischemia. Immunohistochemistry. CD34.

RESUMO

Introdução: Recentes progressos feitos na bioengenharia de enxertos cardíacos oferecem nova modalidade terapêutica para a regeneração do tecido cardíaco pós-infarto do miocárdio. O CD34 é marcador que expressa todas as células precursoras hematopoiéticas e endoteliais, e funciona como fator de adesão celular. O anticorpo que correspondente a este marcador é utilizado na imunoistoquímica para avaliar a formação de novos vasos e a presença de células-tronco.

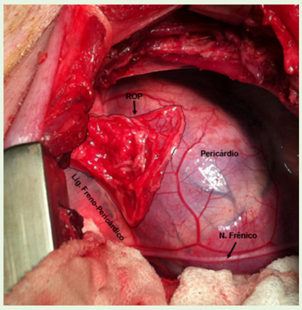
Objetivo: Avaliar a eficácia da omentopexia na neovascularização e células-tronco.

Métodos: Revisão colhendo informações publicadas em plataformas virtuais selecionadas (SciELO – Scientific Electronic Library Online, Google Scholar, Pubmed e Scopus). A busca iniciou-se por descritores relacionados ao tema, identificados por meio do DeCS/MESH nos seguintes descritores: "isquemia miocárdica; revascularização miocárdica; omentopexia; imunoistoquímica; CD34; células-tronco" e seus equivalentes em inglês: "stem cell; myocardial ischemia; myocardial revascularization; omentopexy; immunohistochemistry; CD34". Foram lidos pelo título e resumo, com busca AND ou OR seguindo-se da leitura na íntegra daqueles com maior relação ao tema. Foram incluídos o total de 23 artigos.

Resultados: O omento maior tem propriedade clínica marcante em conter sítios de danos teciduais. Ele aumenta seu volume tecidual em resposta às partículas estranhas e inflamatórias envolvendo diversas células imunomoduladoras com células progenitoras, em um processo chamado "ativação do omento".

Conclusão: A cárdio-omentopexia associada à abrasão mecânica e perfurações miocárdicas, mostra ser eficiente na indução de neovascularização. O omento maior promove células-tronco - confirmadas pelo CD34 -, demonstrando grande potencial como futura terapêutica para restaurar áreas de miocárdio isquêmico.

DESCRITORES: Isquemia miocárdica. Revascularização miocárdica. CD34. Células-tronco.



Pericardial pedicled omental flap (Lig = ligament; N = nerve; ROP = pedicled omental flap

Central Message

Recent advances in cardiac graft bioengineering offer a new therapeutic modality for the regeneration of cardiac tissue after myocardial infarction and myocardial infarction and myocardial infarction. The antibody corresponding to this marker is used in immunohistochemistry to assess the formation of new vessels and the presence of stem cells. This review highlights that cardio-omentopexy associated with mechanical abrasion and myocardial perforations has been shown to be efficient in inducing neovascularization

Perspective

The greater omentum promotes CD34-confirmed stem cells, demonstrating great potential as a future therapy to restore ischemic myocardial areas. It has outstanding clinical property, which is to pursue and contain sites of tissue damage. It increases its tissue volume in response to foreign and inflammatory particles. This involves several immunomodulatory cells together with progenitor cells, in a process called "omentum activation".

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INTRODUCTION

Cardiovascular diseases are the leading cause of death in the world today, leading to alarming mortality rates in several populations. According to data from the Unified Health System (DATASUS) and Brazilian Society of Cardiology, it is estimated that 127,513 people died in the country in 2018 due to ischemic heart diseases, out of a total of 395,700 deaths from cardiovascular causes in the same year. In 2017, 379,133 deaths were recorded due to sudden cardiac death in the United States of America, which represents 13.5% of the total deaths in the country, that is, 1 in every 7.4 deaths of Americans in this period. In the world, in 2017, there were approximately 8,930,000 deaths from ischemic heart diseases, out of a total close to 17,800,000 from cardiovascular causes, which increased by 21.1% compared to 2007.[1,2]

The term acute infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of an increase and/or decrease in cardiac troponin values with at least 1 unit above the 99th percentile of the upper limit of normal with at least 1 of the following data: symptoms of myocardial ischemia; new ischemic changes on the electrocardiogram; development of pathological Q waves; imaging showing recent loss of viable myocardium or wall region as movement abnormality in a pattern consistent with ischemic cause. Pathological diagnosis is defined as cell necrosis due to prolonged ischemia.[3]

The objective of this review was to evaluate the efficacy of omentopexy as a donor of endothelial progenitor cells in previously infarcted myocardium, by means of immunohistochemical analysis of the presence of CD34.

METHOD

The literature review was carried out by collecting information published on virtual platforms in Portuguese and English. The material was selected from the SciELO – Scientific Electronic Library Online, Google Scholar, Pubmed and Scopus platforms. Initially, a search was carried out for descriptors related to the theme, which were identified through DeCS/MESH using the following terms: "myocardial ischemia; myocardial revascularization; omentopexy; immunohistochemistry; CD34; stem cells" read by title and abstract, with AND or OR search and followed by the full reading of those with greater relation to the theme, ending 25 articles.

DISCUSSION

Pathophysiology of infarction

The first structural changes observed occur 10-15 min after the onset of ischemia, with decreased cellular glycogen, relaxed myofibrils, and sarcomere rupture being observed. Mitochondrial abnormalities are usually seen 10 min after coronary occlusion and occur progressively and can be seen on electron microscopy. It can take hours before it is possible to detect myocardial necrosis in humans, unlike what occurs in animals, where it is possible to identify cell apoptosis within 10 min after the induction of ischemia.

Based on experimental studies, necrosis progresses from the subendocardium to the subepicardium over several hours. This time can be increased by the presence of existing collateral flow, reduced myocardial oxygen consumption, and the presence of intermittency between occlusion and reperfusion. Timely implementation of reperfusion therapies is able to reduce the extent of ischemic injury in the myocardium.

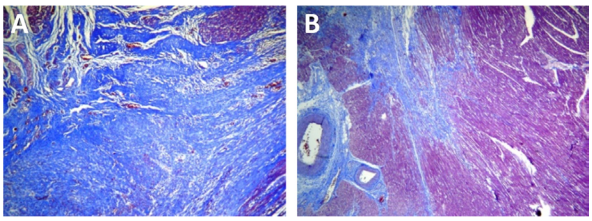
Classification of infarction

It can be classified according to its cause, transmurality and time of evolution

As for the cause[3,4] it can be of 5 types. Type 1 refers to spontaneous infarction due to ischemia resulting from a primary coronary event, such as erosion - with or without rupture -, fissure or dissection of atherosclerotic plaque. Type 2 is infarction secondary to ischemia due to increased oxygen demand or decreased oxygen supply; the causes include: coronary spasm, coronary embolism, anemia, arrhythmias, hypertension or hypotension. Type 3 is sudden death of cardiac origin, usually with symptoms suggestive of myocardial ischemia, but occurring before blood samples are obtained, or shortly before the biomarkers are positive in the blood. Type 4 is infarction associated with percutaneous coronary intervention (4a) or stent thrombosis (4b) or even stenosis after coronary intervention (4c). Finally, type 5 represents infarction associated with the surgical procedure of myocardial revascularization.

As for transmurality5, it can be subendocardial, i.e., ischemia in only 1 subendocardial layer, less than 50% of the thickness of the affected area of the myocardium, or transmural, with ischemic suffering in at least 50% of the thickness of the affected area of the myocardium.

As for the evolution time3, it can be superacute (<6 h); acute (6 h to 7 days); in healing (7-28 days); and healed (≥29 days, Figure 1).



Source: Kubrusly FB et al.[6]

FIGURE 1 — Myocardial tissue infarcted: A) control group, showing extensive myocardial fibrosis; B) cardio-omentopexy group, demonstrating a reduction in collagen deposition in the infarcted area (Masson's trichrome).

Experimental models of myocardial infarction

Several models and experimental studies in animals have been introduced in the academic environment to understand the pathophysiology, in addition to allowing the effectiveness of new treatments to be ascertained given the complexity of the disease.[7] Based on the size of the animals, the models can be classified into small and large animals.

In small ones, studies with rats and rabbits show better cost-benefit than those with larger ones, because they require operations in general with less structure, in addition to allowing a study with a larger number of animals more easily. However, they appear to have lower reproducibility of the results in relation to models with larger animals.[7-9]

In large cases, studies with sheep and pigs are more complex in terms of time and cost. They require more sophisticated procedures that require trained teams and more advanced equipment, as well as special shelter for each animal. However, they have advantages because they have anatomy, energy consumption, tension in the ventricular wall, heart rate and vascular lumen similar to those found in humans, allowing for more comparable results.[7]

Technique with open transthoracic operation

A great advantage is the direct access to the heart and its visualization with greater control over the occlusion site. It is also possible through this technique to analyze cardiac contractility, coronary flow, and metabolic parameters more easily. The limitations of this method are high mortality and morbidity, which can hinder the evaluation of outcomes if not minimized.[7,10]

Technique with minimally invasive percutaneous intervention

Although it does not favor direct visualization, all coronary branches can be observed through fluoroscopy. As disadvantages, the costs of devices and prostheses, the radiation emitted during the procedure and the performance of cardiopulmonary resuscitation maneuvers that are less effective than those performed in the open operation can be mentioned.[10,11]

Ventricular remodeling

After infarction, if there is a long time of ischemia, it is possible that more than 1 billion cells lose their vitality and viability in response to this aggression. The mammalian heart has a variable capacity for regeneration after suffering ischemic injury for a long time, which can range from an adequate response to wound healing to a process in which the lost cells are replaced by fibrotic tissue followed by adverse cardiac remodeling that evolves with impaired systolic function.[12,13]

Once the necrosis process begins, the death of myocytes triggers an inflammatory response. The healing process can be divided into 3 phases. First, there is a pro-inflammatory wave along with a component of degradation of the extracellular matrix, in order to reduce the amount of necrotic debris. Then, the anti-inflammatory and pro-reparative phase follows with the objective of reducing the inflammatory process and stimulating mesenchymal cells in the extracellular matrix deposits to carry out the healing process. And, finally, the maturation phase, where the repairing cells are quiescent and removed. Several cells are involved in this coordinated response, including cardiac myocytes, neutrophils, macrophages, fibroblasts, endothelial cells, and nerve cells.[12,14]

Systolic dysfunction is related to the persistent inhibition of contractile proteins, requiring at least 20 min of ischemia so that these proteins can no longer regenerate spontaneously.[14]

Cardiac fibrosis is divided into 2 parts after the occurrence of the infarction: restorative and reactive fibrosis. The restoration is the one that occurs at the first moment, to prevent the rupture of the heart chamber. However, mechanical stress together with paracrine hormonal response leads to the expansion of this fibrosis in areas remote to the infarction area, which is reactive fibrosis, which alters the compliance of the cardiac chamber and increases ventricular stiffness, compromising contractility and systolic function. This entire area of fibrosis can also lead to abnormalities of cardiac electrical conduction, predisposing to re-entry arrhythmias, such as sustained ventricular tachycardia, bundle branch blocks, among other electrical disorders, which contribute to the risk of sudden death.[13,14]

Coronary artery bypass grafting procedures

In the last 20 years, 2 methods have stood out in obtaining post-infarction coronary artery bypass grafting: percutaneous coronary intervention and coronary artery bypass grafting. The first is established as a good alternative in acute patients, especially with ST-segment elevation, with favorable anatomy, and in some non-diabetic patients with multiple lesions, but with favorable anatomy. The latter, in turn, has been preferred in cases of multiple affected vessels or extensive damage, lesions of the left main coronary artery, unfavorable anatomy, diabetes mellitus, and/or multiple affected arteries, unless there are comorbidities, high surgical risk, or low post-procedure survival expectancy.[15,16]

Greater omentum

A functional organ

It is large, flat adipose tissue that rests on the surface of intraperitoneal organs, mainly on the small and large intestines. In addition to adipose reserve, the greater omentum plays a key role in immunoregulation and tissue regeneration.[17]

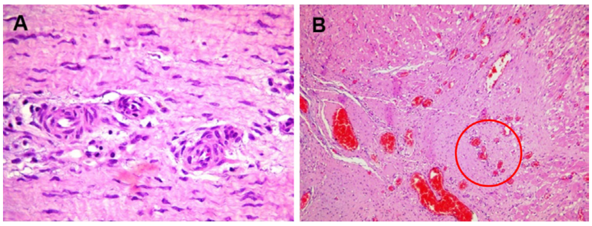
Immune regulation by it is done by units called "Milky spots" that derive from the phagocytic immune system and are composed of 70% macrophages, 10% B lymphocytes, 10% T lymphocytes, in addition to a small percentage of mast cells and stromal cells. These units are formed around a glomerular knot-like structure of blood vessels.[18]

It has outstanding clinical property, which is to pursue and contain sites of tissue damage. It increases its tissue volume in response to foreign and inflammatory particles. This involves several immunomodulatory cells together with progenitor cells, in a process called "omentum activation".[17]

The activated omentum becomes a rich source of fibroblast growth factors (b-FGF) and endothelial growth factors (VEGF), also expressing markers of mature progenitor cells, such as SDF-1a, CXCR4, WT-1, as well as pluripotent biomarkers of embryonic pluripotent stem cells, such as Nanog, Oct-4, SSEA-1.[17,18]

Angiogenesis and neovascularization

Angiogenesis is defined as the formation of new blood vessels from previously existing vessels. It has a sequence that involves increased vascular permeability mediated by vascular endothelial growth factor (VEGF), followed by extravasation of plasma proteins associated with vasodilation. The vascular coverage is then reduced and through the action of proteases such as cathepsins, metalloproteases, among other enzymes, the extracellular matrix also ruptures. At this point, epithelial cells migrate and proliferate. The process is completed by the reunion of endothelial cells that form a vascular lumen and a new basement membrane (Figure 2).[19]



Source: Kubrusly FB et al.[6]

FIGURE 2 — Myocardial infarcted tissue: A) control group, showing absent or minimal neovascularization; B) cardio-omentopexy group, demonstrating exuberant neovascularization (H&E).

A key property of the omentum is that it allows angiogenesis in structures to which it is grafted. Researchers have already demonstrated that human omentum endothelial cells (HOME cells) express angiogenic peptides such as FGF-β and VEGF, which are key factors for neovascularization. This process of neoangiogenesis allows providing vascular support and blood supply to the tissues, promoting the healing process in ischemic and inflamed tissues.[17]

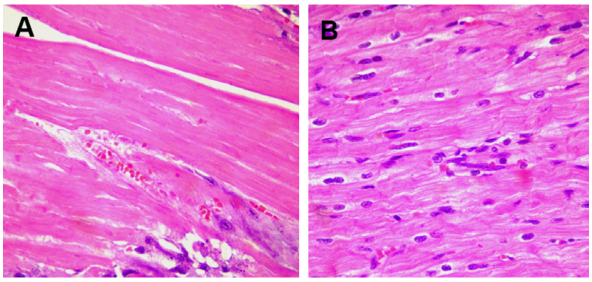
In this context, the neovascularization of cardiac ischemic areas becomes decisive for increasing survival, and both angiogenesis and the circulation of endothelial progenitor cells (EPCs) during vasculogenesis would be essential for the evaluation of the response to ischemia; there is growing evidence that increased mobilization of EPCs increases ischemic tissue neovascularization and may be clinically relevant in the setting of tissue ischemia.[20]

It has been observed that the omentum is an extraordinary source of angiogenic factors such as VEGF and FGF-β. Specifically, CD34-positive cells of the human omentum may be responsible for promoting angiogenesis and synthesizing growth factors that facilitate the revascularization of the affected tissue.[17]

Experiments on the function of CD34 indicate that it is expressed in endothelial cells and may play a role in leukocyte adhesion during the inflammatory process; it has been hypothesized that CD34 may be used in the localization of stem cells, both in the bone marrow and in other tissues. Primitive cells of the hematopoietic system can be identified by immunohistochemical method using anti-CD34 antibodies. The presence of this marker induces the perception of vascular neoformation and provides an evaluation of the nutrition of the tissue studied.[21]

Healing and regeneration

Grafting of the greater omentum showed that not only does it differentiate into mesenchymal lineage cells, but also into cells of ectoderm and endoderm origin, including cardiomyocytes, lung epithelial cells, hepatocytes, neurons, and pancreatic cells (Figure 3).[17]



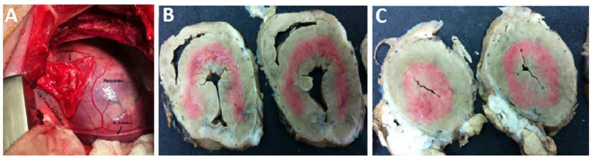
Source: Kubrusly FB et al.[6]

FIGURE 3 — Myocardial infarcted tissue: A) control group, showing extensive coagulative necrosis; B) cardio-omentopexy group, demonstrating minimal myocardial damage, longitudinally arranged myocytes, ovalate and centralized nucleus (H&E).

In a clinical trial conducted with rats after induction of cardiac hypertrophy, omentopexy was able to reduce the mass of the heart muscle, improve the left ventricular function, including the ejection fraction, preserving its systolic function. In the control group, a significantly larger diameter of cardiomyocytes was found in the histology, in addition to larger areas of fibrosis, demonstrating the healing and regeneration capacity of the heart muscle that omentopexy presents.[22]

Use of the greater omentum in cardiac and thoracic surgery

It has been used as a support in the challenges of myocardial regeneration, overcoming vascularization deficiency and favoring the grafting of bioengineered tissues. Its regenerative properties have been explored in surgical techniques, such as omental transposition, where the tissue is extended or surrounded by the omentum to promote healing, as occurs in the cardio-omentopexy technique (Figure 4).[22,24,25]



Source: Kubrusly FB et al.[6]

Lig = ligament; N = nerve; ROP = pedicled omental flap

FIGURE 4 — Experimental aspects of cardio-omentopexy: A) thoracic transposition of the pedicled omental flap and its positioning on the pericardial surface for measurement and accommodation, before pericardiotomy; B) macroscopic transverse aspect of the heart of the animal not submitted to cardio-omentopexy where myocardial thinning is observed); C) cross-sectional macroscopic aspect of the heart of animals submitted to cardio-omentopexy, observing preserved myocardial thickness

Cardiac bioengineered tissues include a variety of approaches, where they can use skeletal muscle cells, cells derived from the omentum itself, atrial tissue, liver tissue, uterine tissue, and stem cells. The omentopexy technique favors the grafting of these cells.[22,23]

In a systematic review, Wang et al.[22] reported 17 clinical trials where, with cardiac omentopexy, greater density of arteriolar vessels and capillaries, increased angiogenic markers, increased blood flow, decreased cardiac remodeling, and improved ventricular function were found. However, they warned of the need for more studies to understand the mechanisms of these events and their clinical applicability.

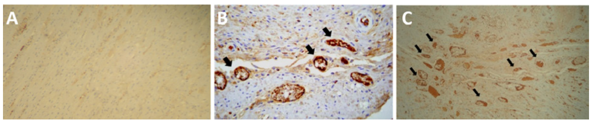
Immunohistochemical marker CD34

CD34 is a membrane glycoprotein with a molecular weight of approximately 110 kDa. It is expressed in all hematopoietic cells, endothelial cells, embryo fibroblasts, and some cells of fetal nervous tissue and in adults.[21] It functions as a cell adhesion factor, and also acts by mediating the binding of hematopoietic stem cells to the extracellular matrix or stromal cells.

Human vascular endothelial cells newly isolated after ischemic events, for example, are CD34 positive (CD34+) cells. CD34 expression has also been detected during angiogenesis in human tumors, during embryogenesis, and in wound healing. According to Ribeiro et al.[,] the presence of CD34+ cells works as a cell adhesion factor and can be used in the localization of stem cells, both in the bone marrow and in other tissues.

Studies indicate that the CD34 of endothelial cells can help in the adhesion of leukocytes to the inflammatory process. It is also hypothesized that it can be used in the location and identification of stem cells, both in the bone marrow and in the tissues. Progenitor and primitive cells of the hematopoietic system can be identified by immunohistochemical method and the use of anti-CD34 antibodies. The presence of this marker indicates vascular neoformation.

During the initial period of angiogenesis developed by ischemia, cells known as TIP Cells develop and migrate to the extracellular matrix and are immediately followed by CD34+ cells that begin their differentiation into endothelial cells, initiating the development of vascular shoots (Figure 5).



Source: Kubrusly FB et al.[6]

FIGURE 5 — Immunohistochemical analysis of CD 34 expression in infarcted myocardial tissue in pigs submitted to cardio-omentopexy: A) control group; B) and C) arrows mark neoangiogenesis, and unmarked regions are bluish

Kubrusly[6], in an experimental study studying the subject, showed that the quantification of the presence of CD34 in the slides leads to the belief that the cells that are being donated by the omentum are the stem cells of real interest to the ischemic myocardium. The time of development of neovascularization, demonstrated by the euthanasia in 30 days of its animals, evidenced the rapid and diffuse differentiation that these cells are capable to achieve.

CONCLUSION

Cardio-omentopexy, associated with mechanical abrasion and myocardial perforations, has been shown to be efficient in inducing neovascularization. The greater omentum induces neovascularization due to the presence of stem cells, recognized through CD34 labeling, demonstrating great potential as a future therapy to restore ischemic myocardial areas.

Authors' contributions
Conceptualization: Fernando Bermudez Kubrusly
Research: Fernando Bermudez Kubrusly
Methodology: Luiz Fernando Kubrusly
Project administration: Jurandir Marcondes Ribas-Filho
Writing (original draft): Luiz Fernando Kubrusly
Writing (proofreading and editing): All authors

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