Terapia Celular em Cardiologia

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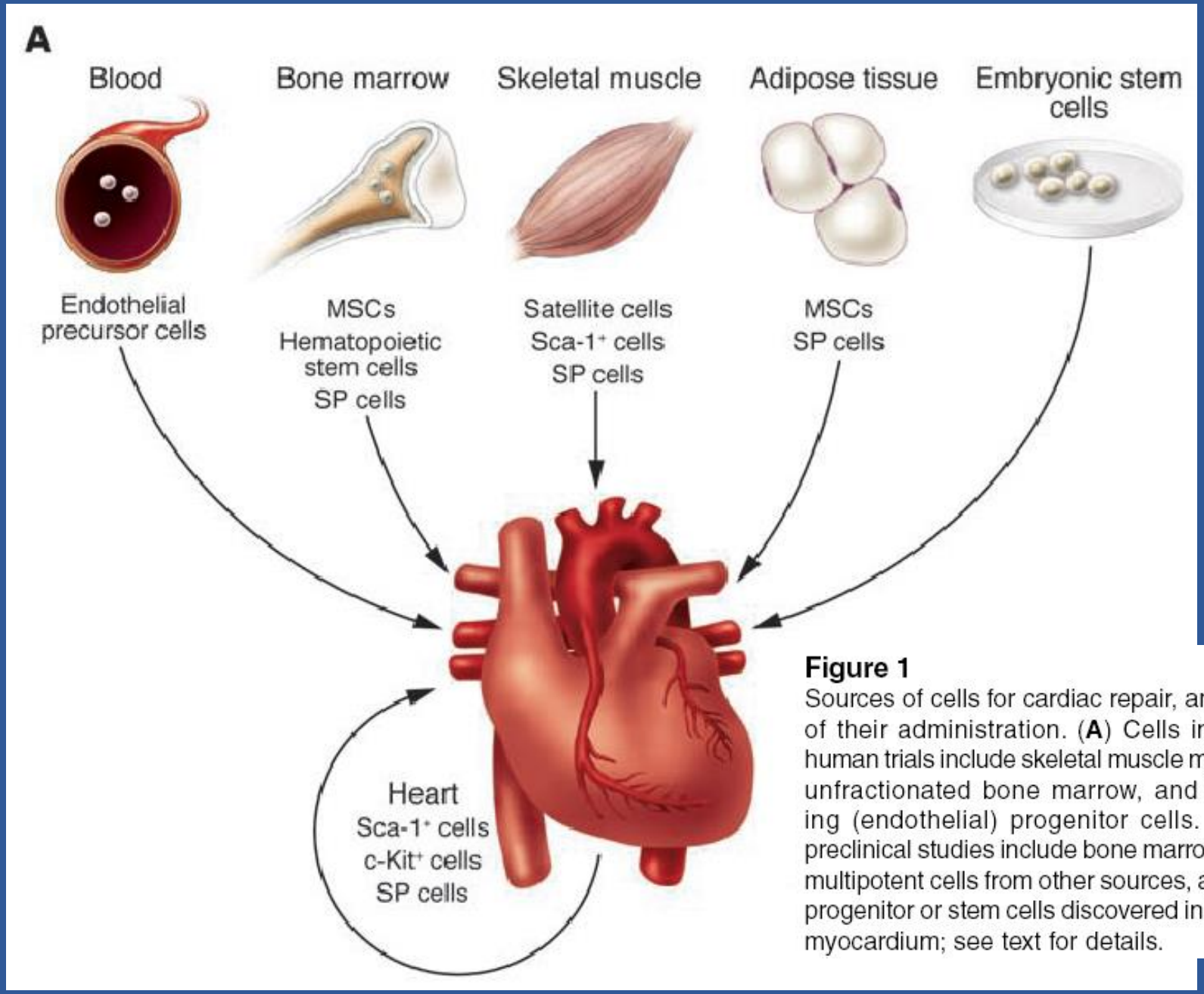
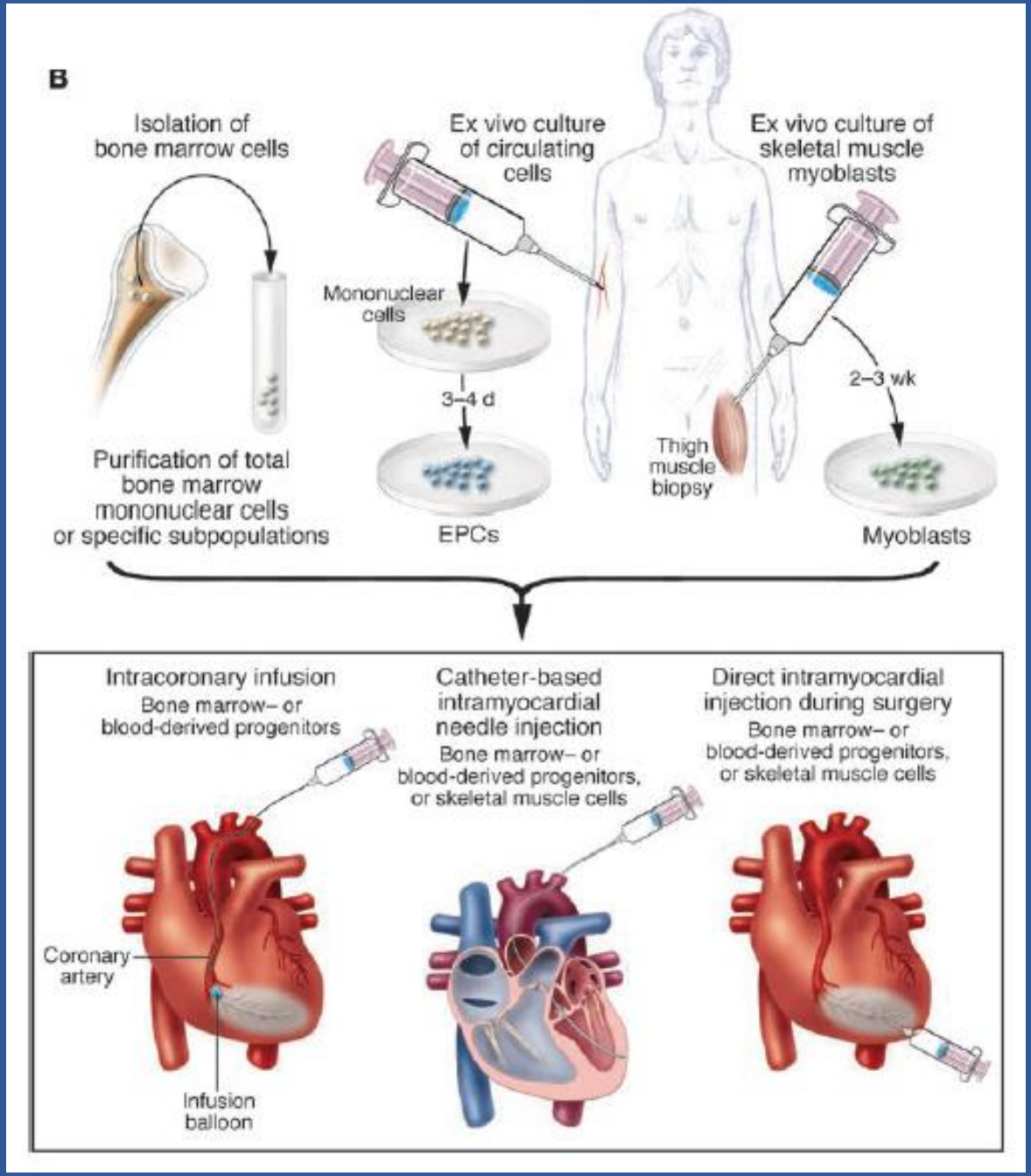


Figure 1
Sources of cells for cardiac repair, and routes of their administration. (**A**) Cells in current human trials include skeletal muscle myoblasts, unfractionated bone marrow, and circulating (endothelial) progenitor cells. Cells in preclinical studies include bone marrow MSCs, multipotent cells from other sources, and novel progenitor or stem cells discovered in the adult myocardium; see text for details.

Dimmeler, S; Zeiher, A. M and Schneider, M.D. The Journal of Clinical InvestigationVol. 115; 03, march 2005



(**B**) Existing trials use intracoronary delivery routes (over-the-wire balloon catheters), intramuscular delivery via catheters (e.g., the NOGA system for electromechanical mapping), or direct injection during cardiac surgery. Not represented here are the theoretical potential for systemic delivery, suggested by the homing of some cell types to infarcted myocardium (39), and strategies to mobilize endogenous cells from other tissue sites to the heart.

Dimmeler, S; Zeiher, A. M and Schneider, M.D. The Journal of Clinical Investigation Vol. 115; 03, march 2005

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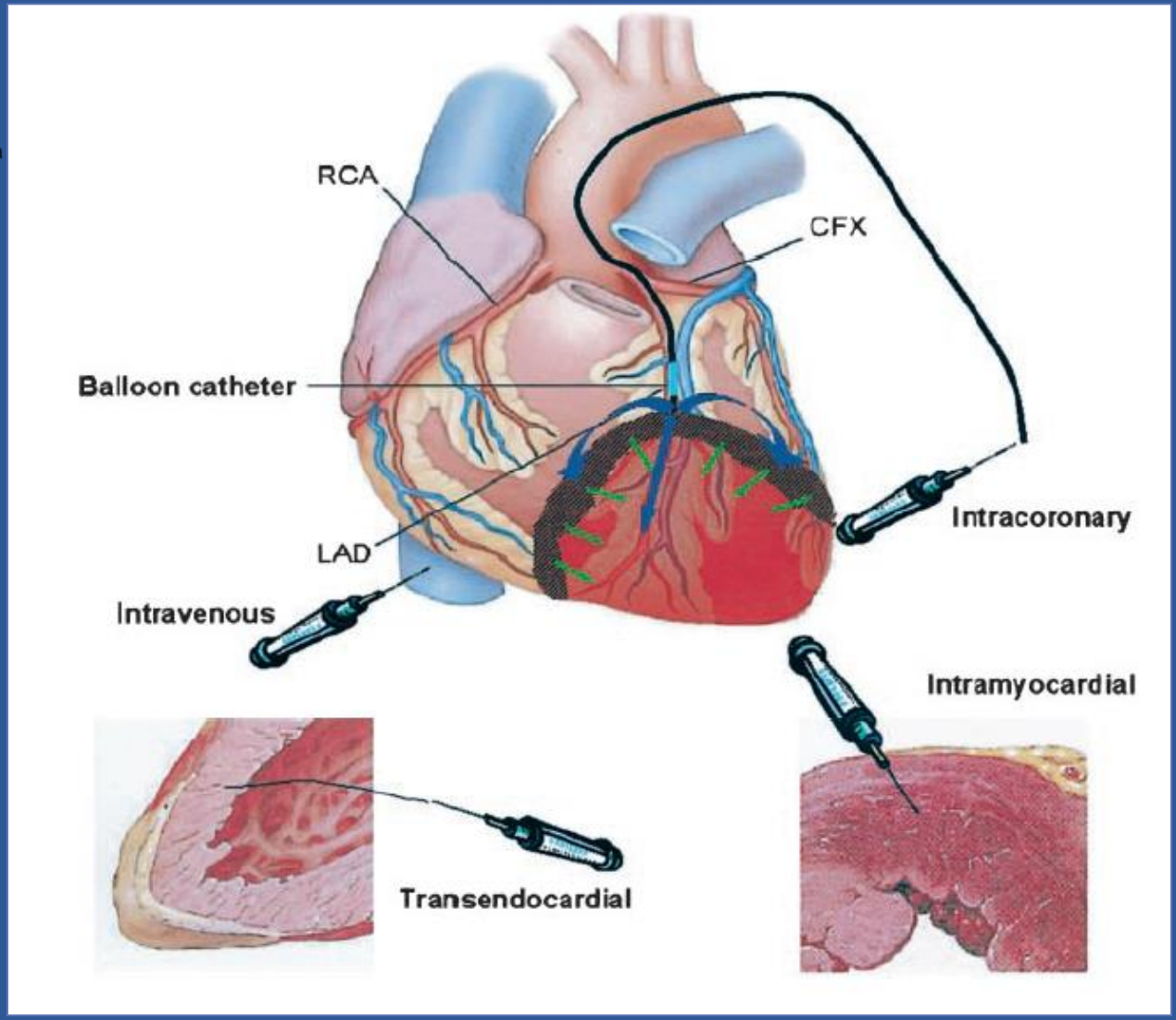


Delivery options for stem cell transfer modalities to the heart. The red colored area represents apical lesion of the left ventricle by myocardial infarction. The balloon catheter is localized in the infarct-related artery and is placed above the border zone of the infarction. Blue and green arrows suggest the possible route of cell infusion and migration into the infarct. The 2 small figures depict the transendocardial and intramyocardial route of administration. RCA indicates right coronary artery; LAD, left anterior descending coronary artery; and CFX, circumflex artery.

Circulation. 2003;107:929-934

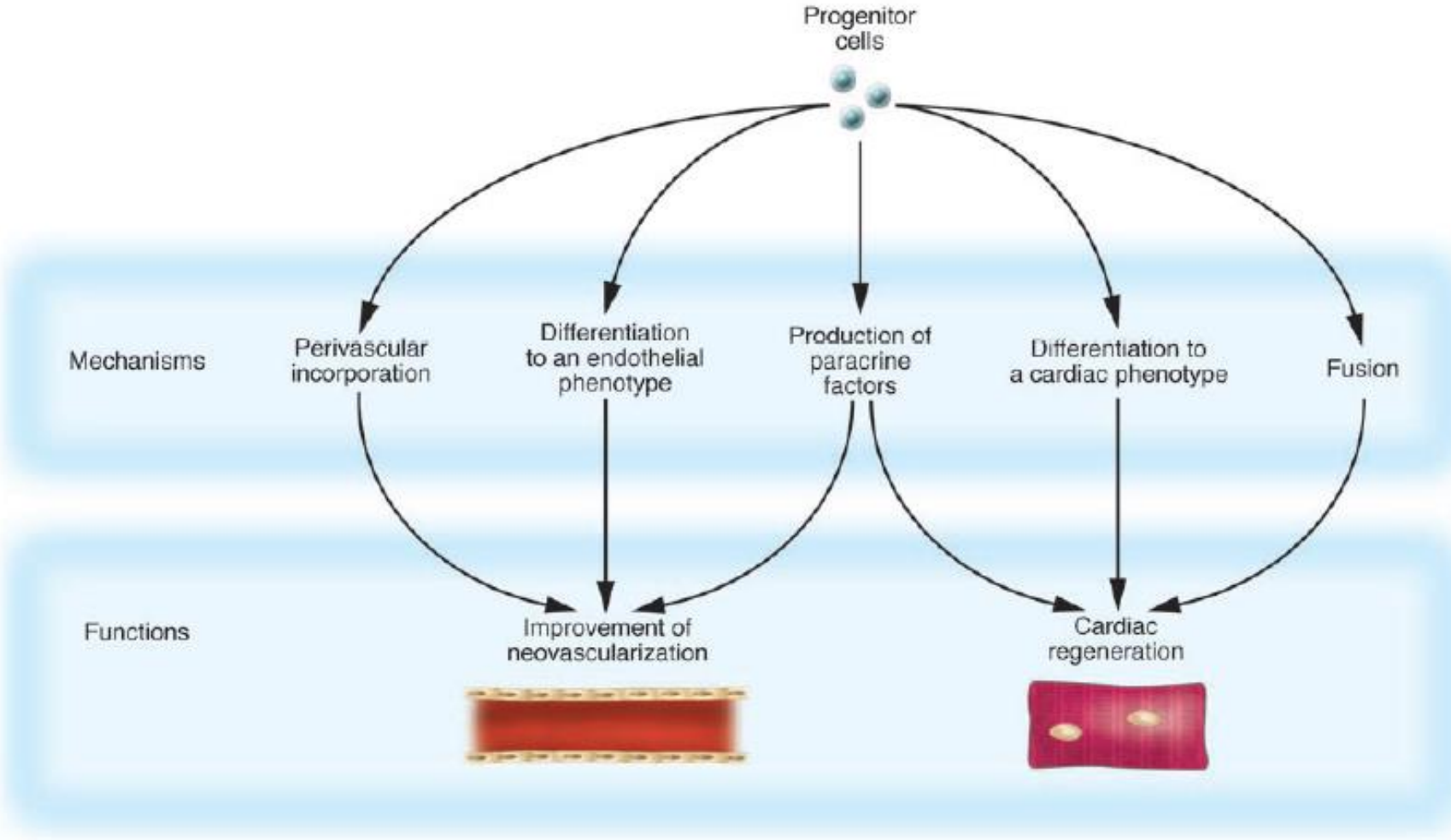


Figure 2

Mechanisms of action. Progenitor cells may improve functional recovery of infarcted or failing myocardium by various potential mechanisms, including direct or indirect improvement of neovascularization. Paracrine factors released by progenitor cells may inhibit cardiac apoptosis, affect remodeling, or enhance endogenous repair (e.g., by tissue-resident progenitor cells). Differentiation into cardiomyocytes may contribute to cardiac regeneration. The extent to which these different mechanisms are active may critically depend on the cell type and setting, such as acute or chronic injury.

Dimmeler, S; Zeiher, A. M and Schneider, M.D. The Journal of Clinical Investigation Vol. 115; 03, march 2005

Aplicações da Terapia Celular em Cardiologia

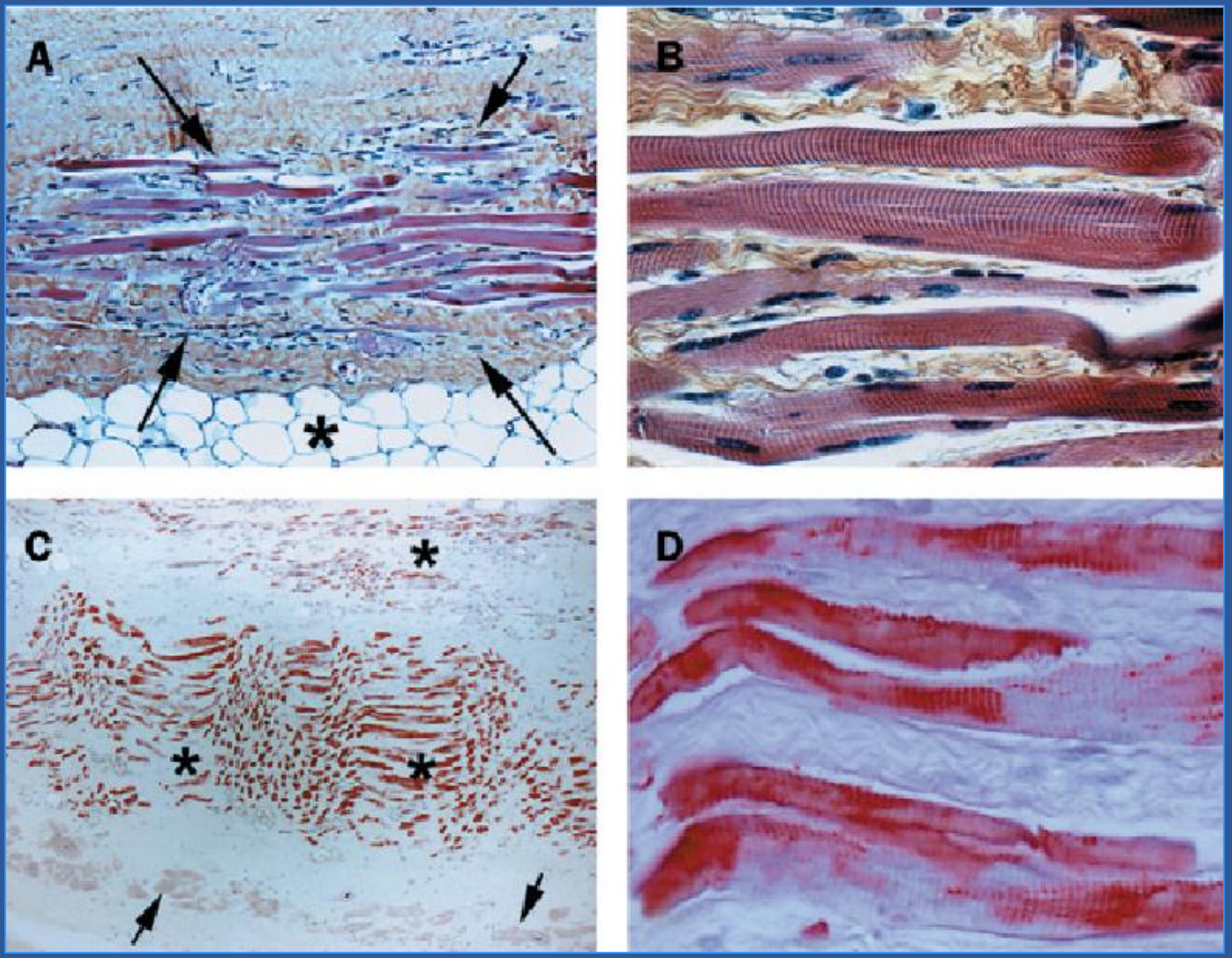
Doença Arterial Coronariana Crônica

- IAM
- Cardiomiopatia Dilatada
- Doença de Chagas

Viability and differentiation of autologous skeletal myoblast grafts in ischaemic cardiomyopathy

Hagège AA, Carrion C, Menasché P et al. Lancet 2003;361:491-92

Relato de caso: mioblastos estriados injetados em fibrose pós-IAM



Serial sections of the engrafted scar area at 17·5 months after injection. Sections stained with haematoxylin and eosin.

A: Arrows show well differentiated subepicardial islets of grafted skeletal myotubes replacing scar fibrosis; asterisk shows epicardial fat (100).

B: Higher magnification shows skeletal myotubes with prominent normal Z bands in myofilaments, and peripheral multiple nuclei in myotubes, without junctions between adjacent grafted cells (400).

C: Immunohistochemistry with MY-32 antibody to fast-twitch skeletal myosin; asterisks show labelled skeletal myocytes by contrast with only lightly labelled remaining cardiomyocytes (arrows) (50).

D: Higher magnification showing the strong signal for fasttwitch skeletal myosin in grafted myocytes (400).

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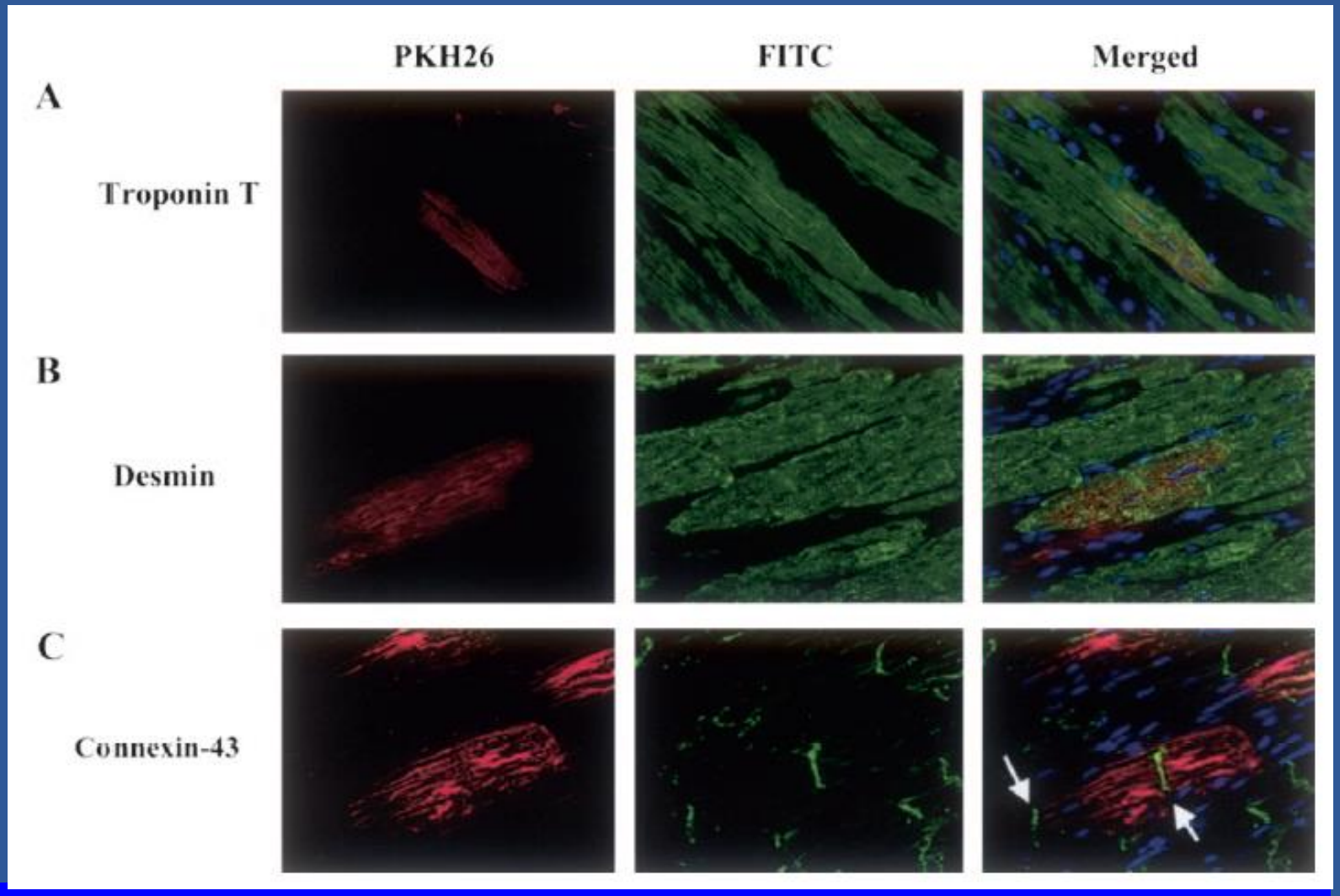
Diferenciação em Cardiomiócitos



Transplantation of Mesenchymal Stem Cells Improves Cardiac Function in a Rat Model of Dilated Cardiomyopathy

Nagaya N e cols, Osaka Circulation 2005;112;1128-35

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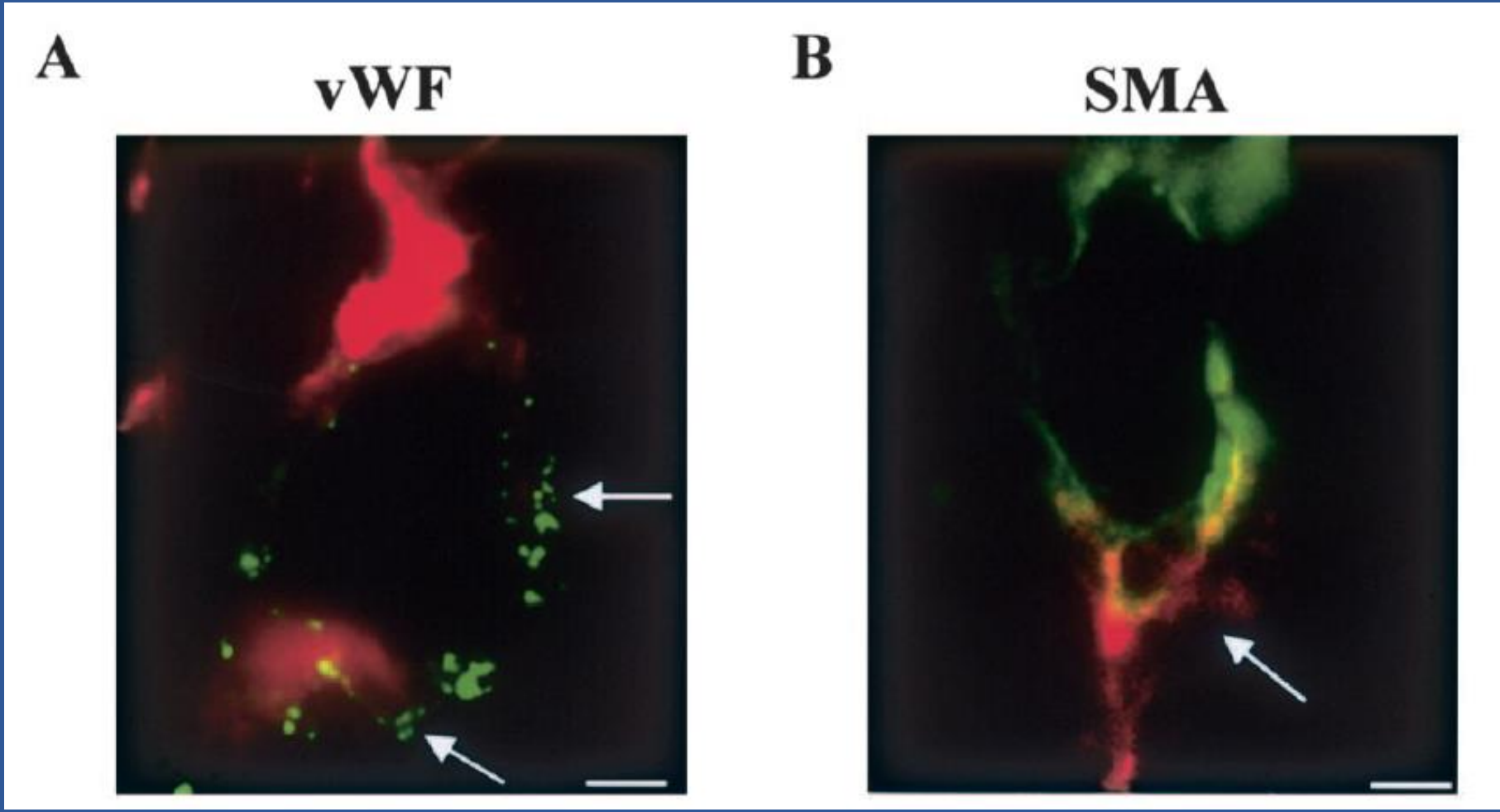
Diferenciação Vascular



Transplantation of Mesenchymal Stem Cells Improves Cardiac Function in a Rat Model of Dilated Cardiomyopathy Nagaya N e cols, Osaka Circulation 2005;112;1128-35

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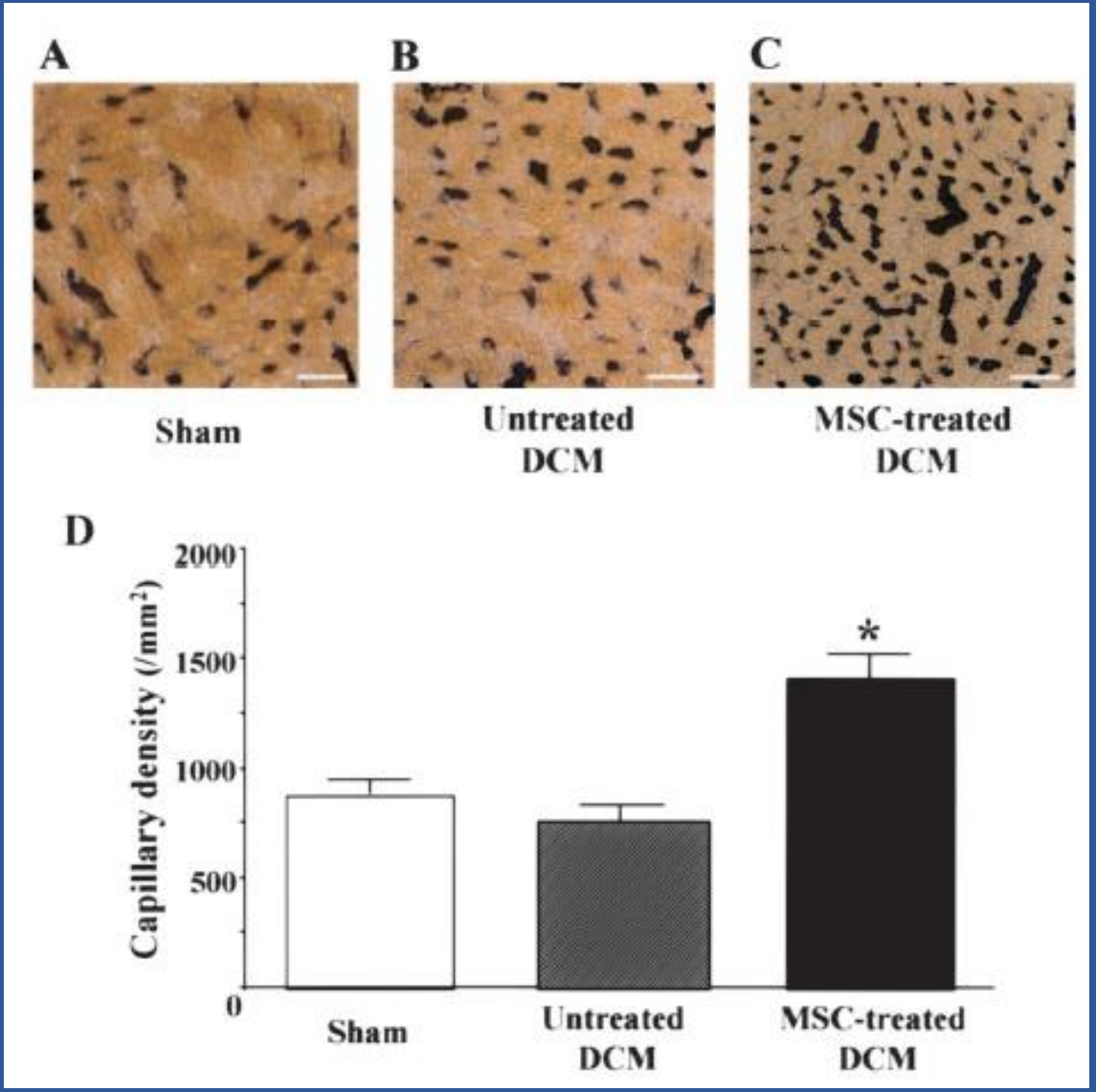
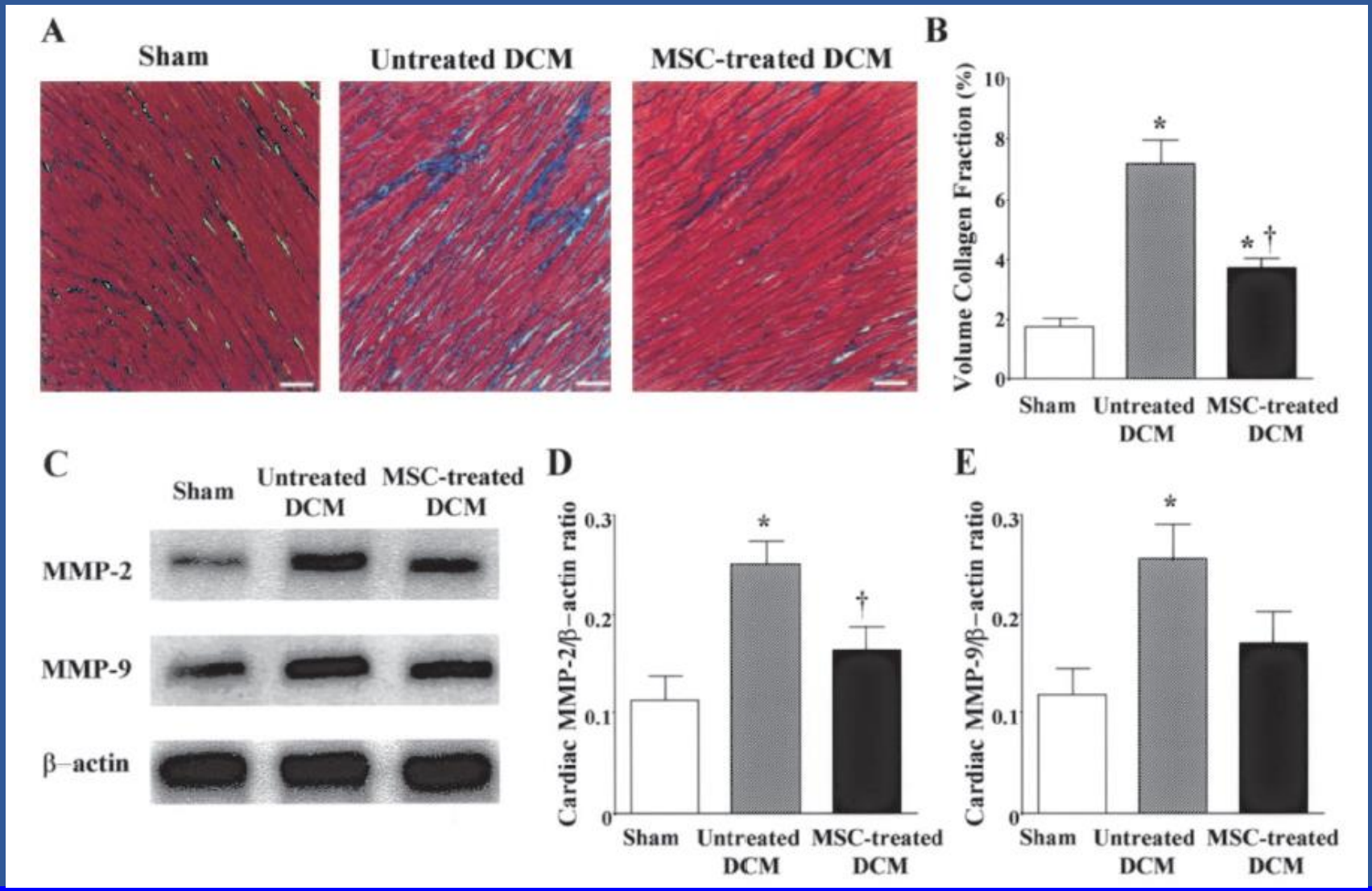
Neovascularização



Transplantation of Mesenchymal Stem Cells Improves Cardiac Function in a Rat Model of Dilated Cardiomyopathy. Nagaya N e cols, Osaka Circulation 2005;112;1128-35

Redução de Fibrose Miocárdica



Transplantation of Mesenchymal Stem Cells Improves Cardiac Function in a Rat Model of Dilated Cardiomyopathy

Nagaya N e cols, Osaka Circulation 2005;112;1128-35

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1. Aspirado da medula óssea (60 a 80 ml)

3 horas antes do início da cirurgia

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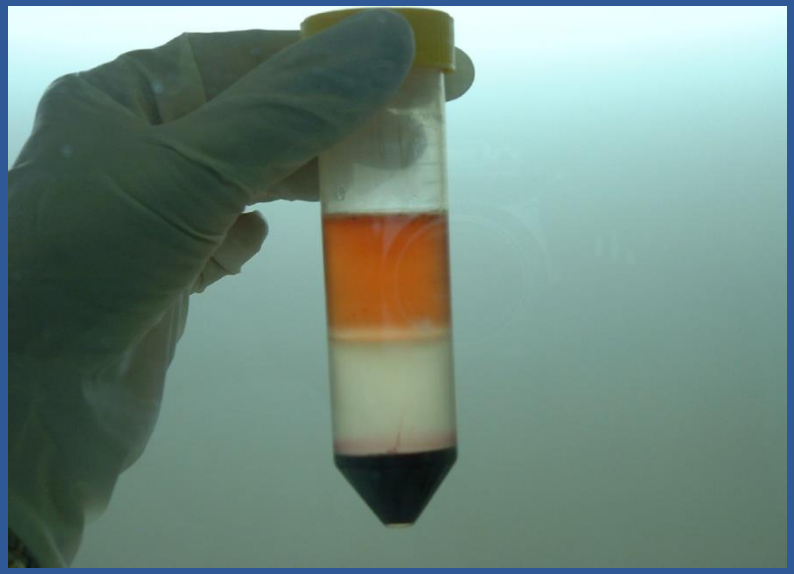

2. Separação da fração mononuclear (1h30-2h)

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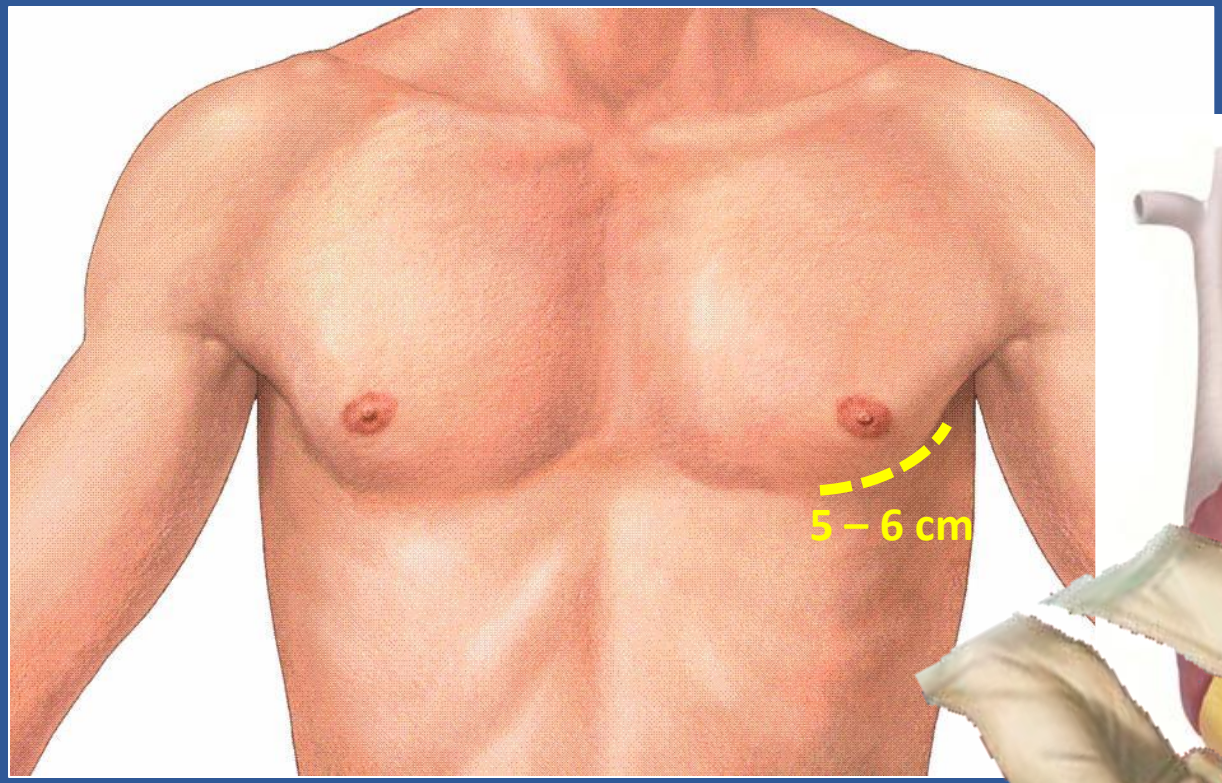
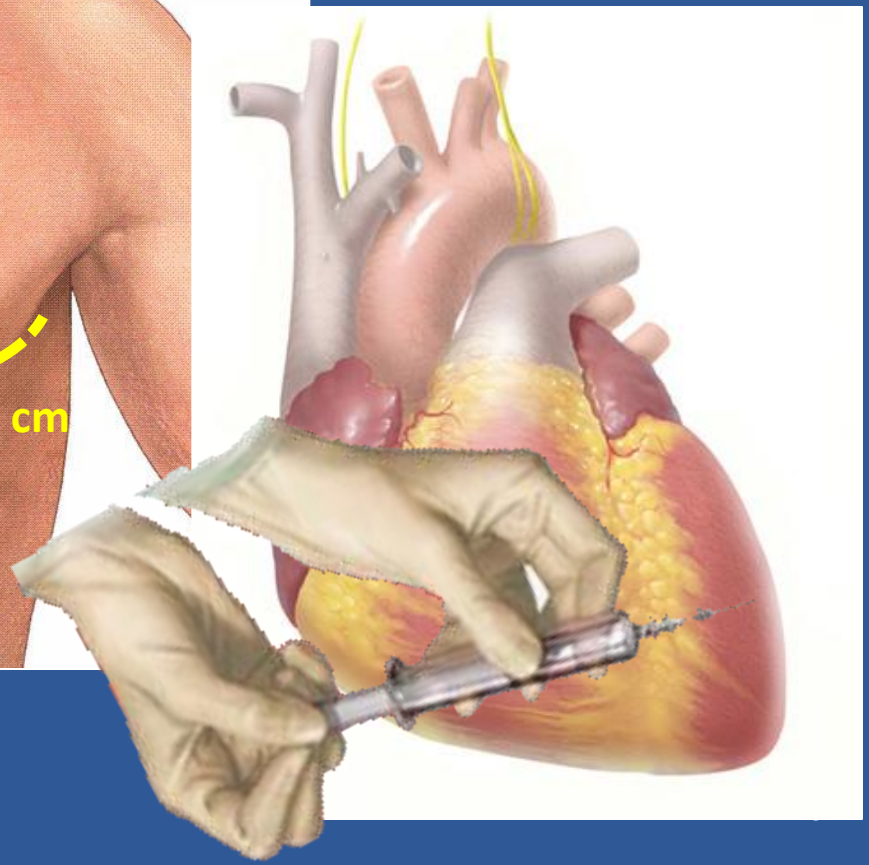
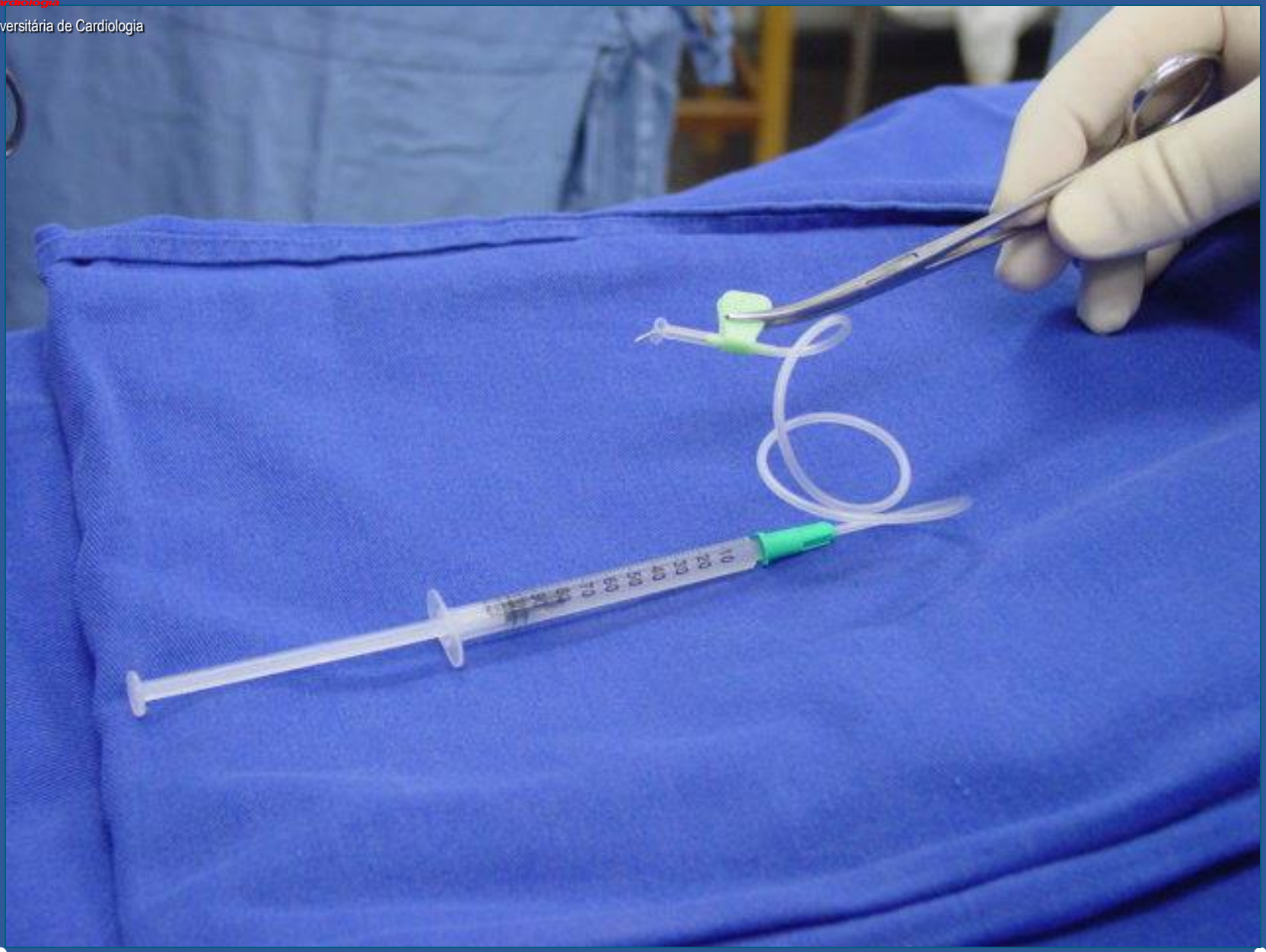
Transplante Autólogo Intramiocárdico de Células Tronco da Medula Óssea na Cardiomiopatia Dilatada Não- isquêmica

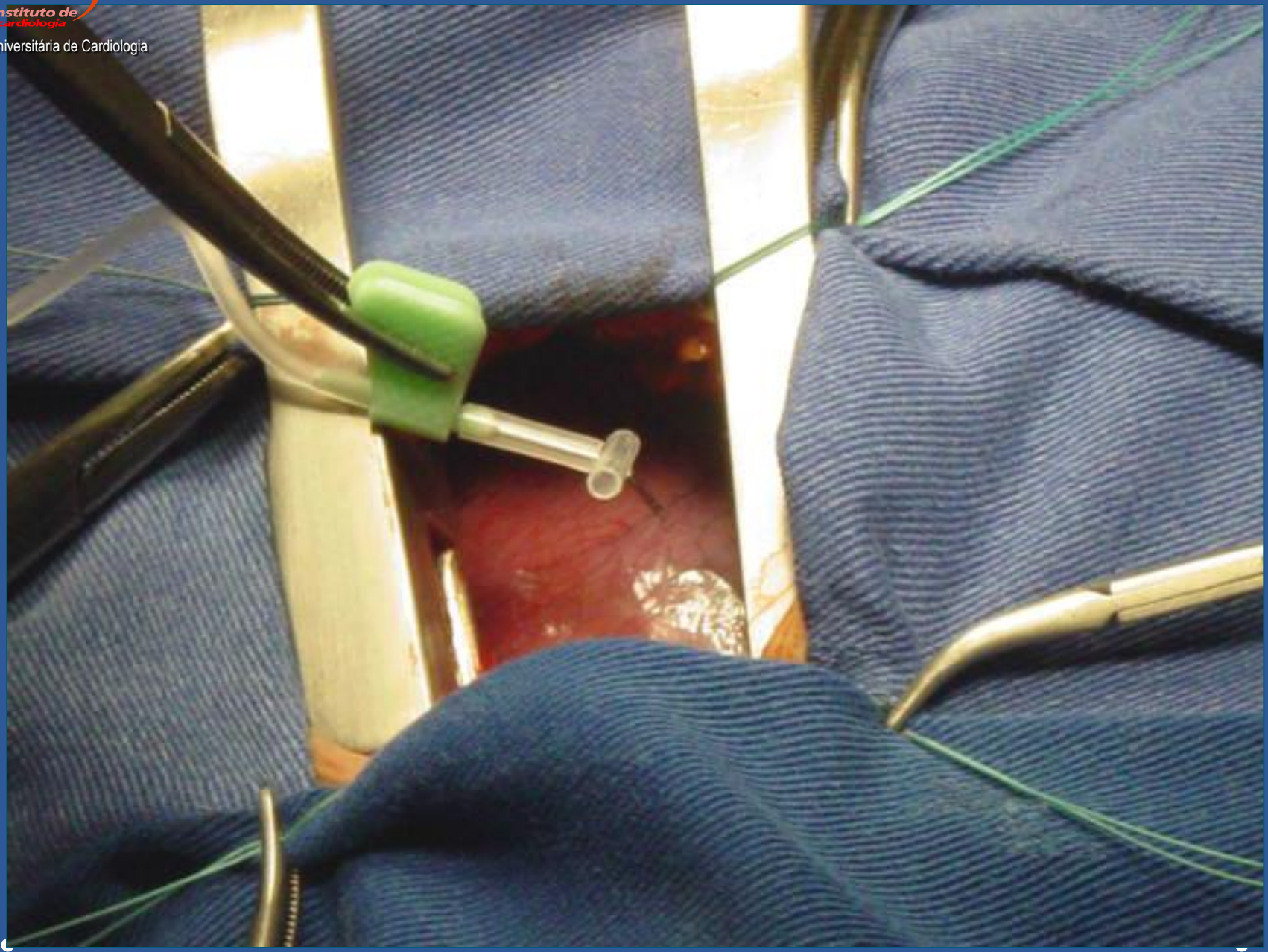




Terapia Celular por Abordagem Cirúrgica na Cardiomiopatia Dilatada



Terapia Celular por Abordagem Cirúrgica na Cardiomiopatia Dilatada



Transplante Autólogo Intramiocárdico de Células Tronco da Medula Óssea na Cardiomiopatia Dilatada Não- isquêmica: Resultados Preliminares de Estudo Prospectivo Randomizado Controlado

Casuística e Método

INCLUSÃO
(1)Doença há mais de 1 ano, classe funcional III ou IV
(2)FE < 35%
(3)Idade < 65 anos

EXCLUSÃO
(1)Arritmia ventricular
(2)Insuficiência valvar mitral
(3)Neoplasia
(4)Doença sistêmica grave

Apoio Edital CT-Biotecnologia MS/DECIT, CNPq, FAPERGS

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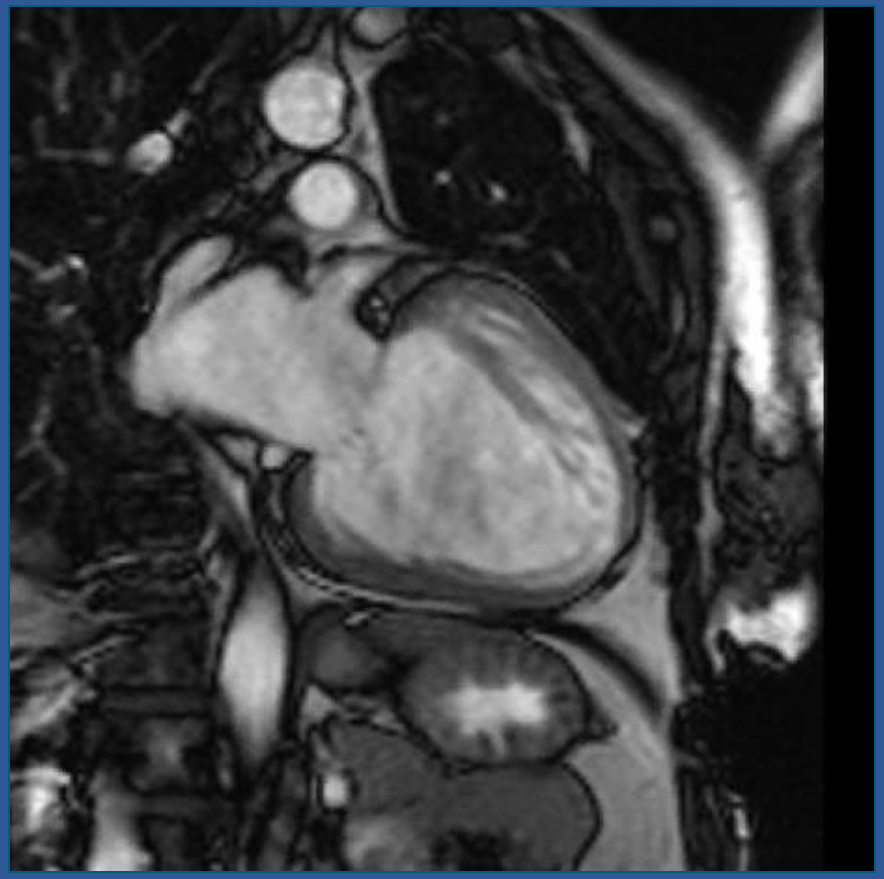
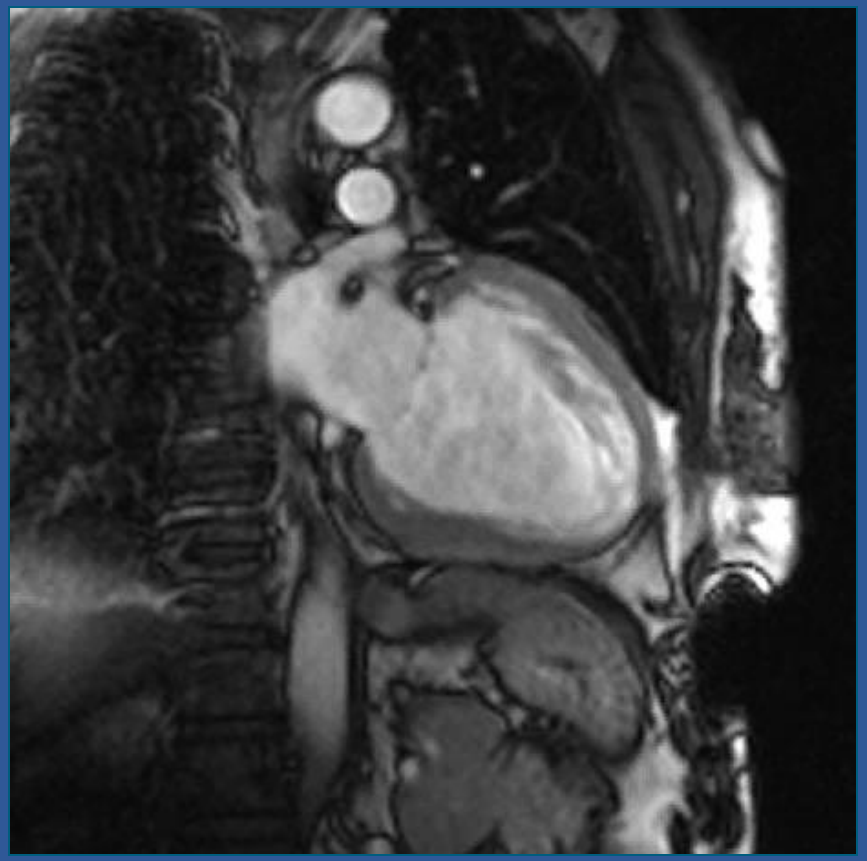
Intramyocardial Bone Marrow Stem Cells Transplantation for Non-ischemic Dilated Cardiomyopathy: 12 Months Follow-up



2 cam- pre



2 cam-post

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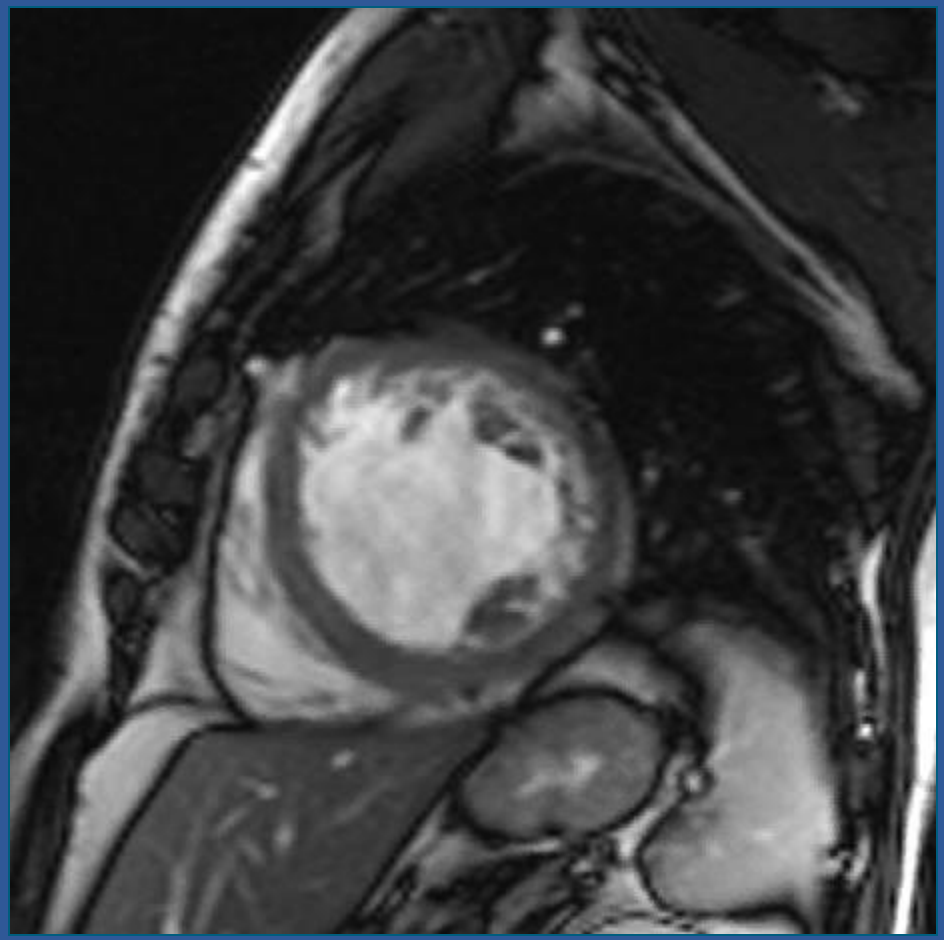

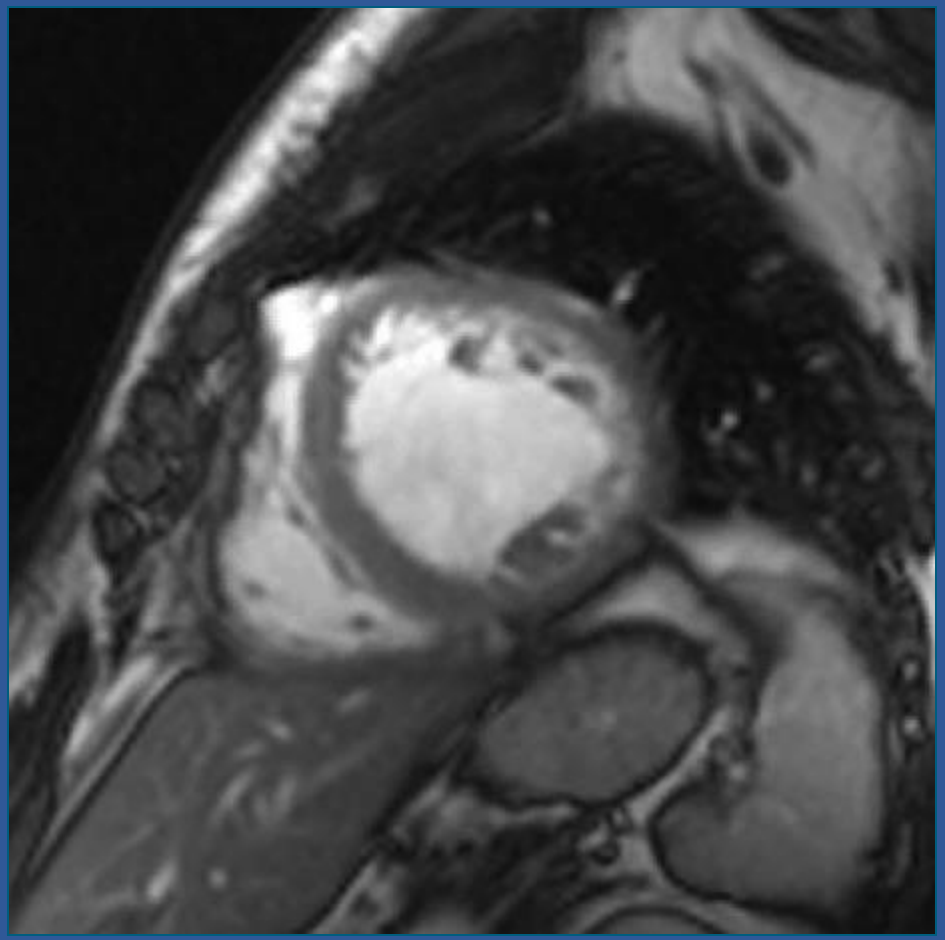

Papillary muscle- pre

Papillary muscle -post

-

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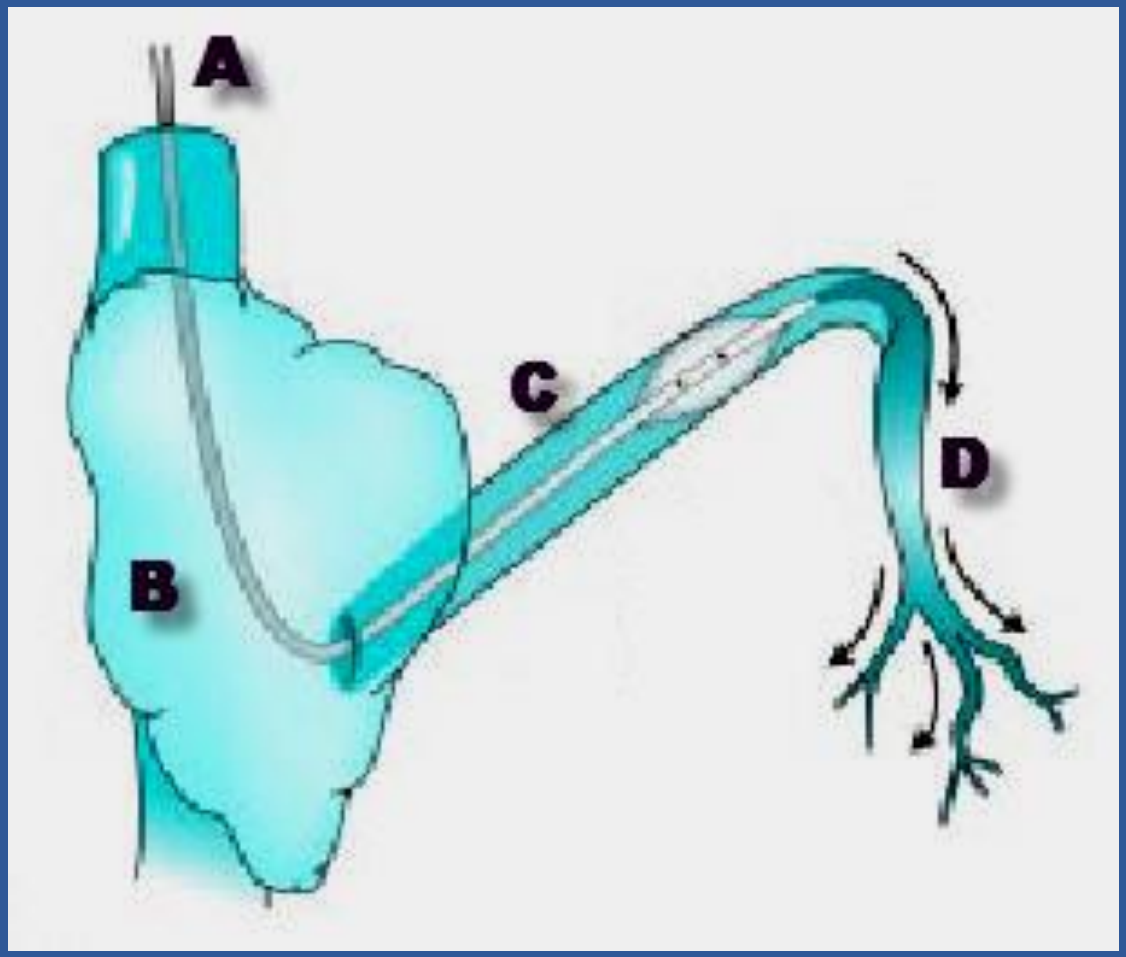
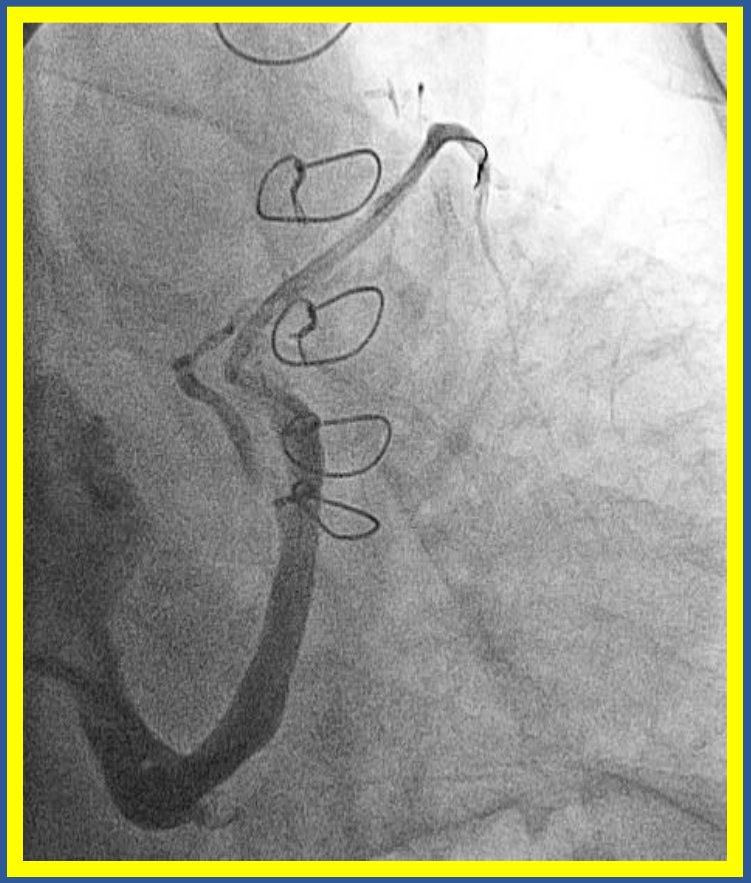
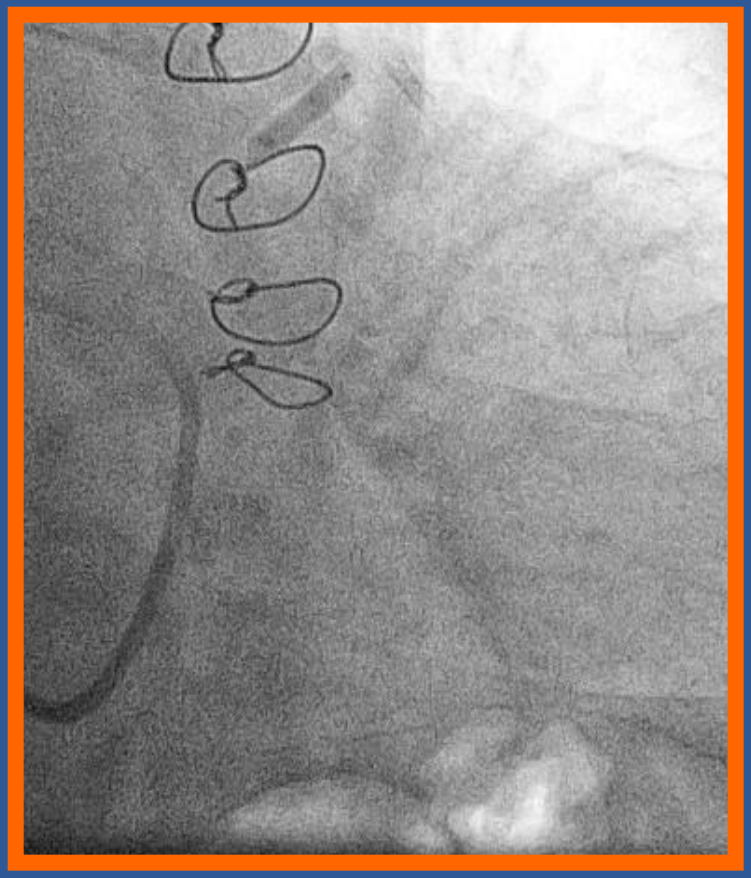

A
B
C
D

1

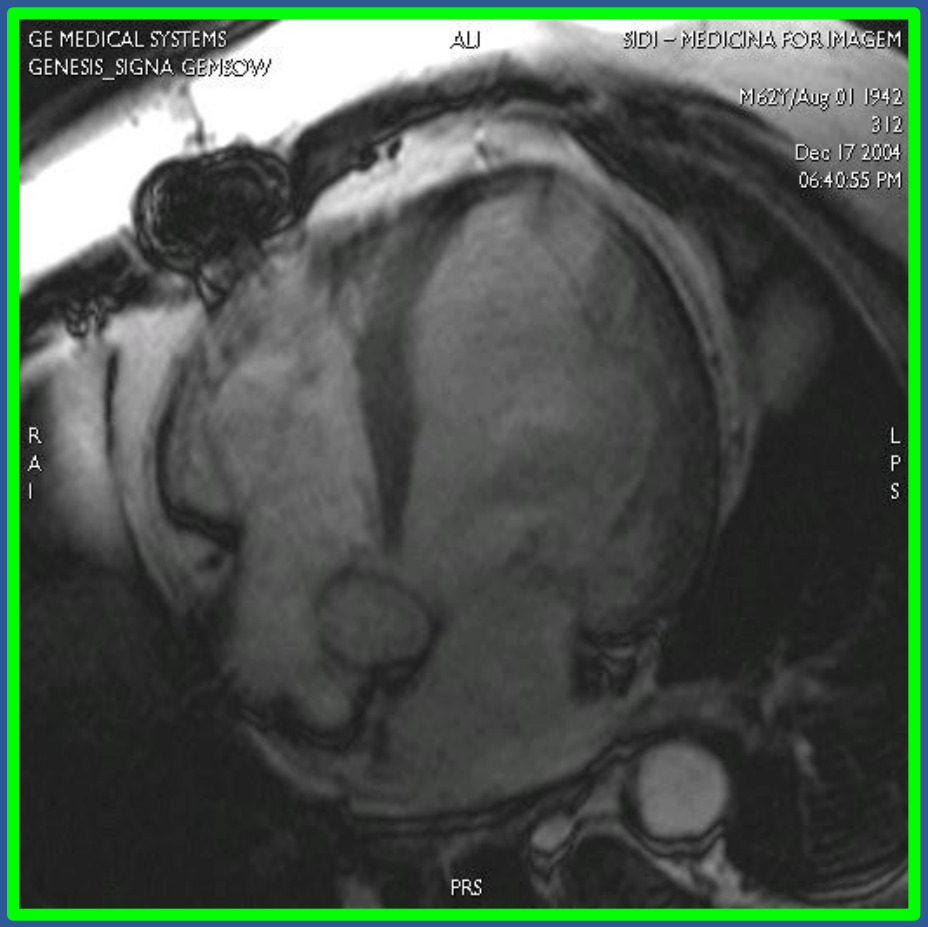
Angiografia do seio venoso com seletivação da veia cardíaca anterior

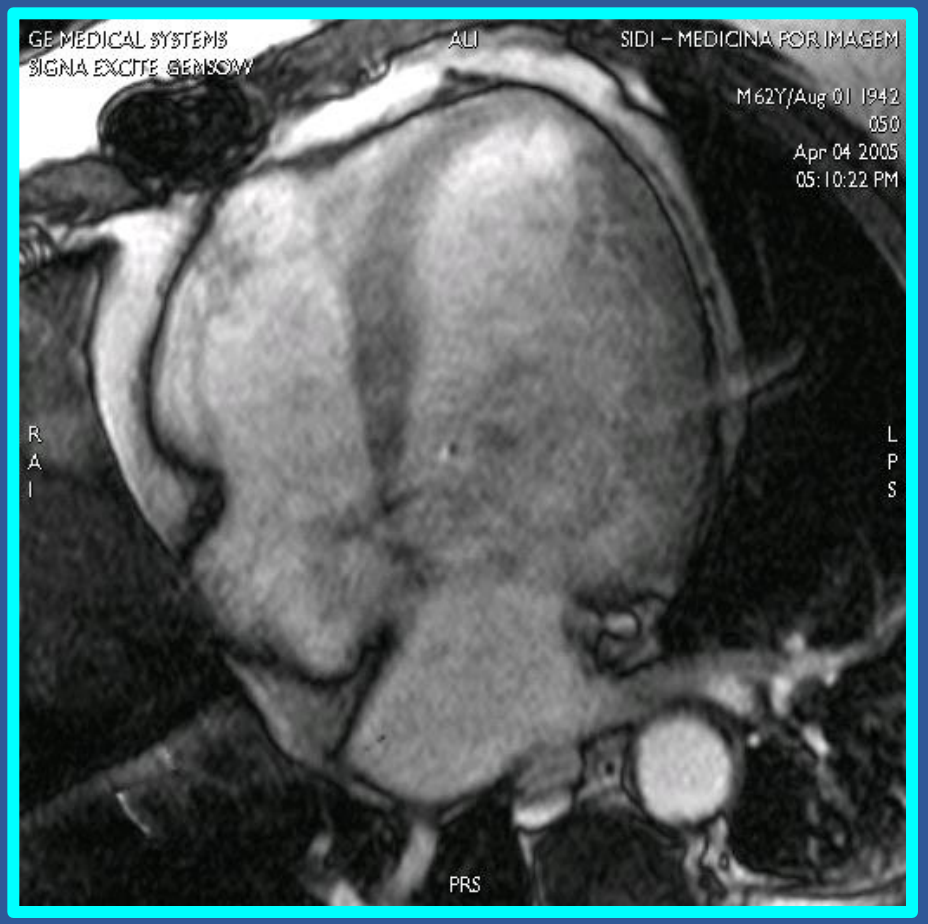




Oclusão temporária da veia cardíaca anterior com infusão de células por perfusão retrógrada

4 Câmaras





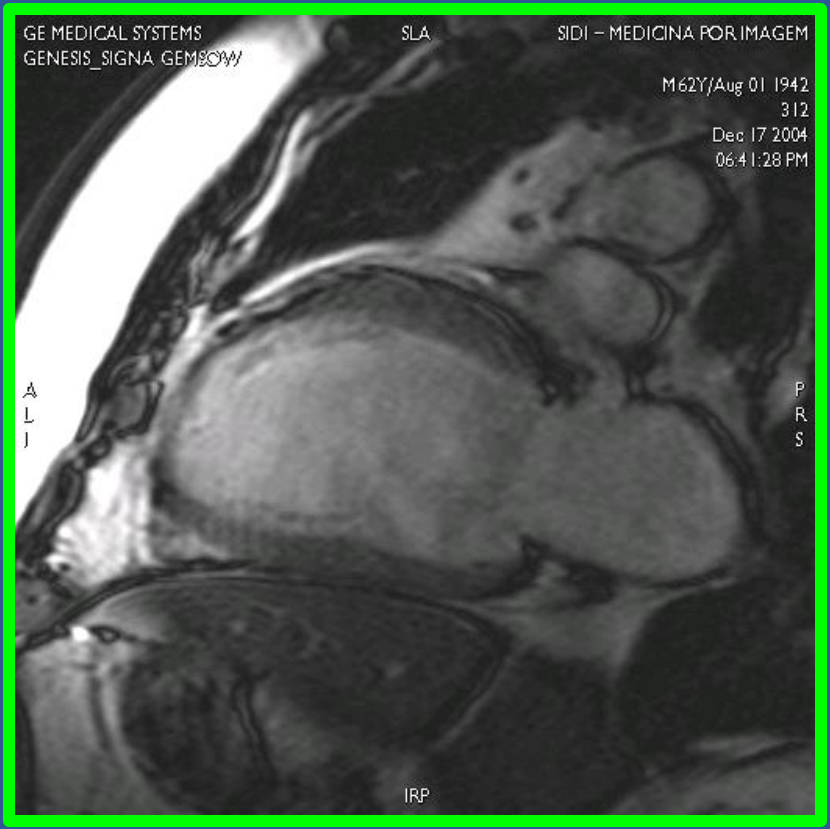
17/12/2004

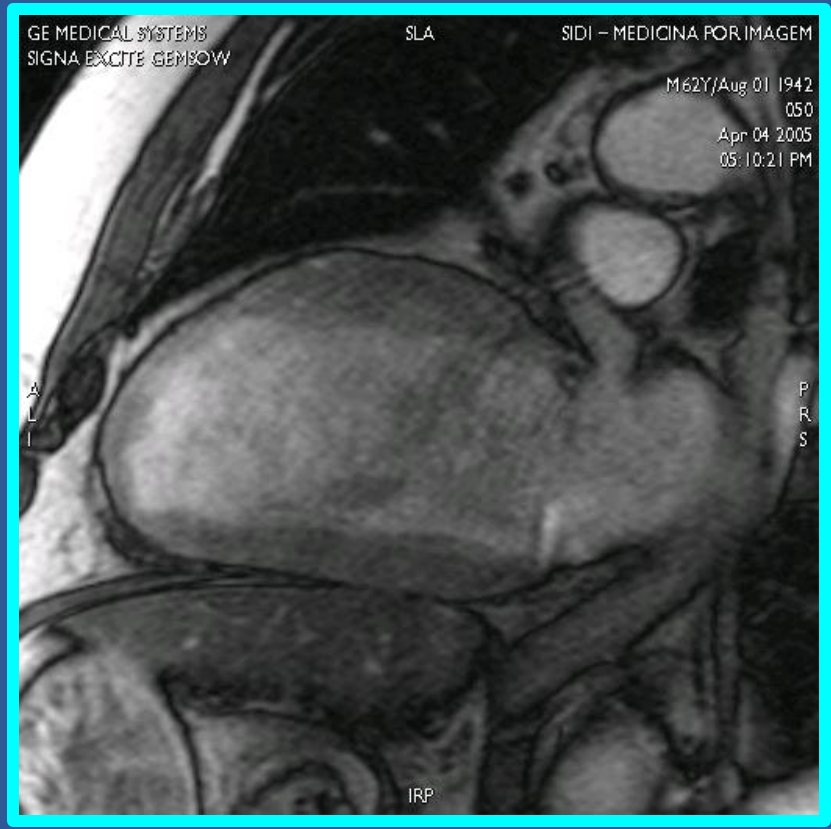
Pré células tronco

04/04/2005

Pós células tronco

2 Câmaras





17/12/2004

Pré células tronco

04/04/2005

Pós células tronco

Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial

- (Stem Cell Infusion in Patients with Ischemic cardiOmyopathy [SCIPIO]) : autologous CSCs for the treatment of heart failure resulting from ischaemic heart disease.
- LVEF increased from 30·3% (SE 1·9) before CSC infusion to 38·5% (2·8) at 4 months after infusion (p=0·001)
- Resultados preliminares

Bolli R, Anversa P e cols. Lancet 2011 Nov 26;378(9806):1847-57

Stem Cell Infusion in Patients with Ischemic cardiOmyopathy (SCIPIO) – Interim Report

Background: Re-growing dead heart muscle after a myocardial infarction (MI) is not currently a treatment option. This trial looks at the use and safety of cardiac stem cells to regenerate tissue in infarcted areas.

Purpose: Safety evaluation of intracoronary cardiac stem cells (CSCs) therapy in humans.

Design: Phase I , randomized, safety/efficacy trial. Control (n=7): No treatment; Study Patients(n=17 ; 14 with 4 month f/u): Autologous cardiac stem cells from the right atrial appendage were re-infused into the heart 4 months after CABG. 4 month and 1 year follow-up results.

Primary Endpoint: Adverse outcomes 1 month after injection and serially going forward (death, ventricular tachycardia, infection, bleeding, MI, stroke, peripheral embolism).

Results:

4 months f/u

Treated at 4 months (n=14): LVEF (3D echo): 30.3 ± 1.9% at baseline; 38.5 ± 2.8% at 4 months after infusion (P = 0.001)
Controls at 4 months (n=7): LVEF (3D echo): 30.1 at baseline vs. 30.2 at 4 months after infusion.

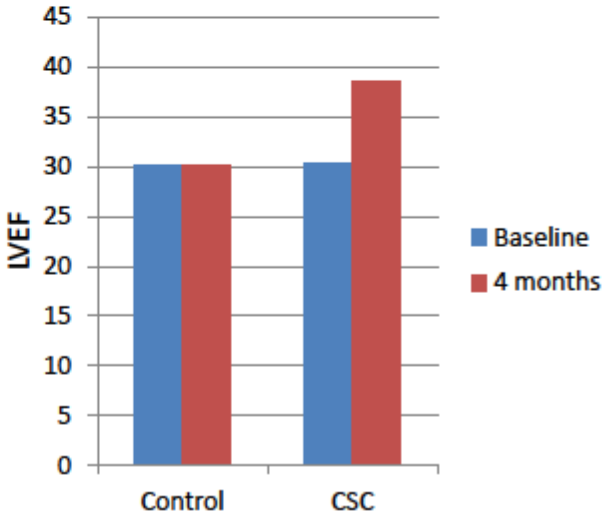
1 Year f/u (n=8)

LVEF increase of 12.3% vs. pre-CSC, P<0.001

MRI results (n=7) – at 4 months

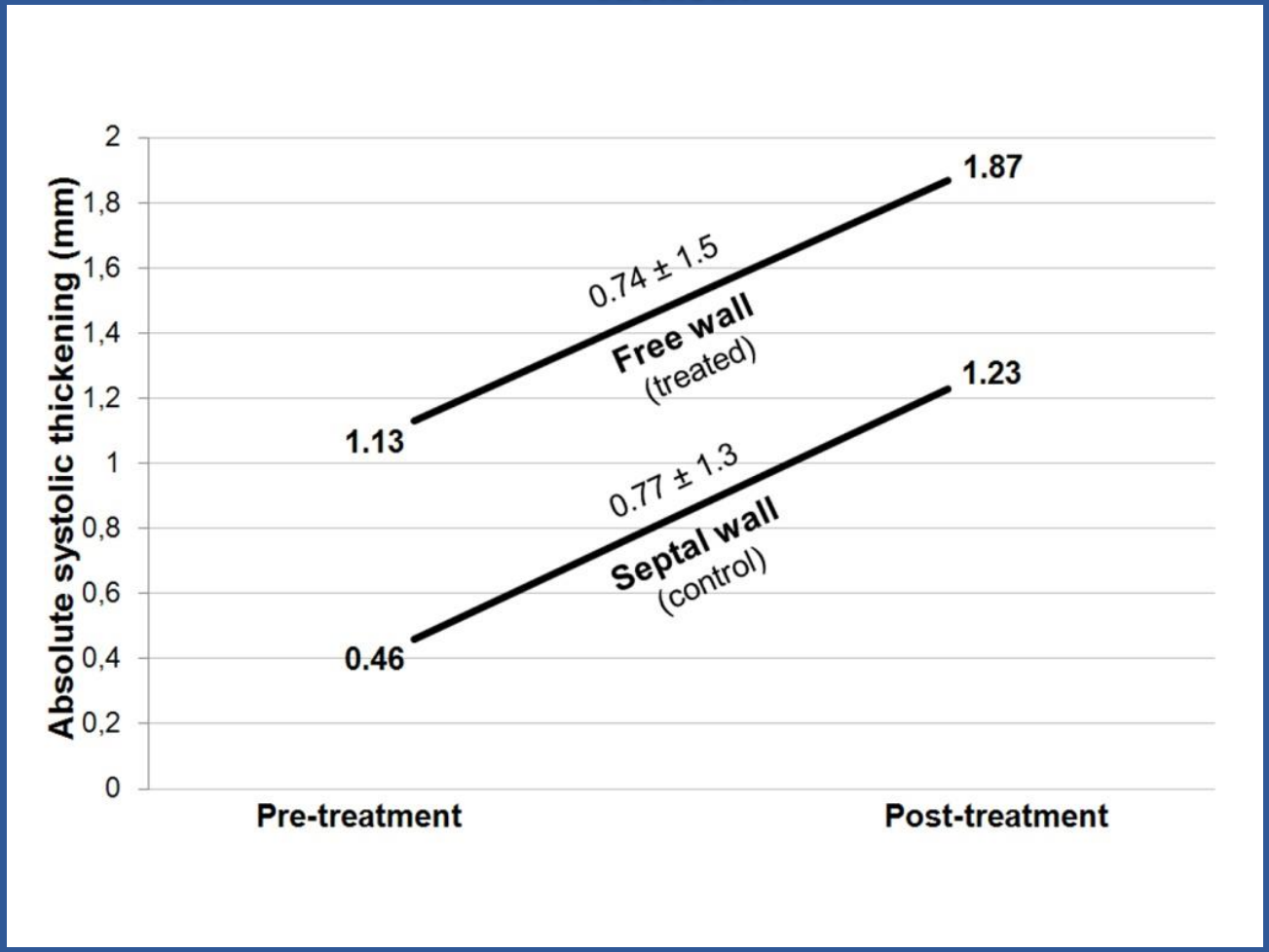
Infarct size decreased: 2.53 baseline vs. 2.21 at 4 months , **P=0.03**

Conclusion: Left ventricular systolic function and infarct size appear to be improved with autologous CSC infusion.



Roberto Bolli, MD AHA Scientific Sessions , 2011, Orlando

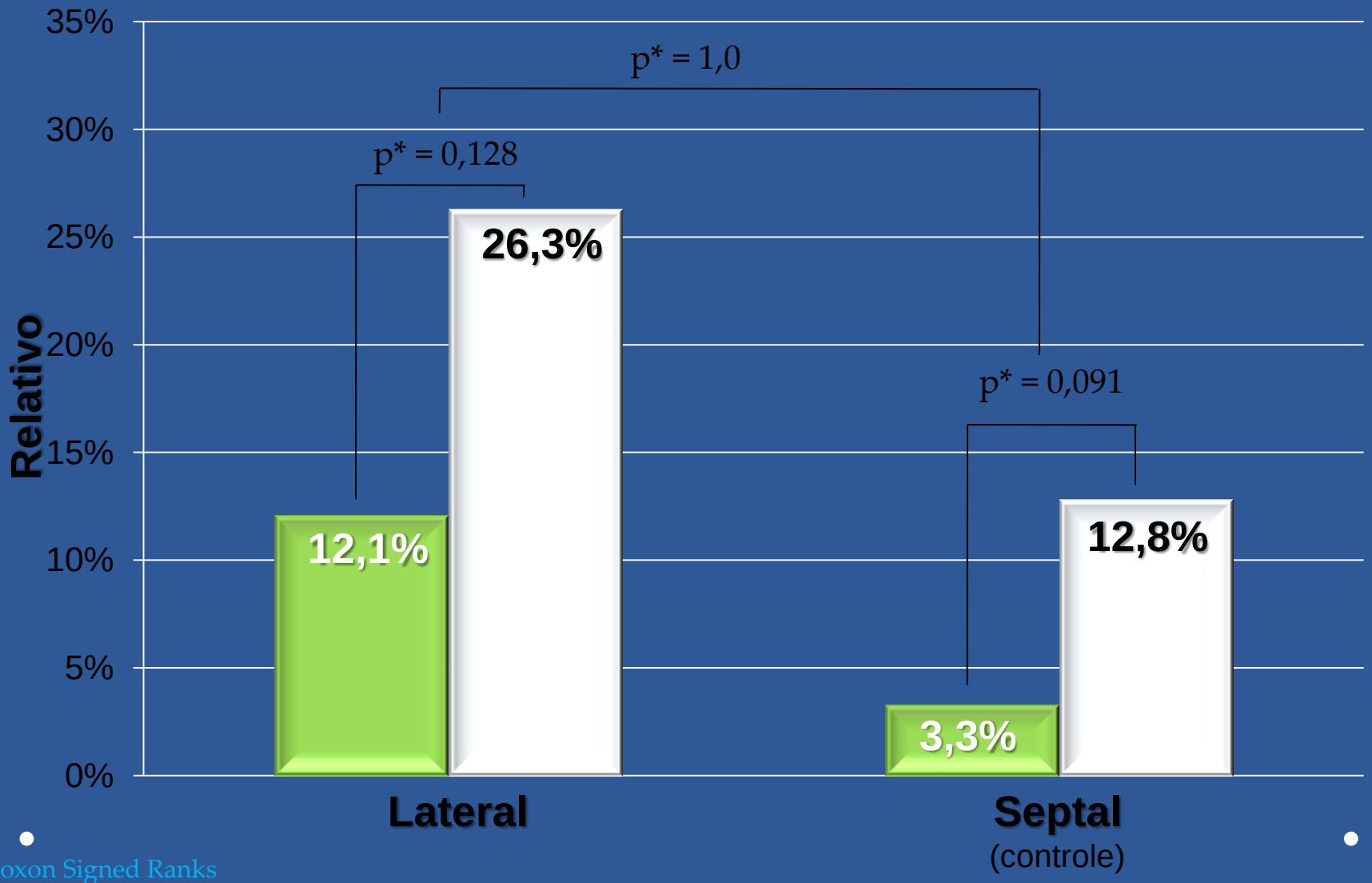
Mononuclear Cells: An Insight over Stem Cells Clinical Mechanism of Action.



Sant'Anna RT, Kalil RA, et al
Cell Transplant. 2010;19(8):959-64

RESULTADOS

Espessamento sistólico



*Wilcoxon Signed Ranks

CONCLUSÕES

O transplante de CMMO na CDNI pode melhorar a função ventricular e essa melhora parece ocorrer através de um efeito global, mesmo em áreas não diretamente tratadas com essas células

Essa observação deve favorecer a hipótese de efeito parácrino, humoral, para explicar o mecanismo de ação das células-tronco

Terapia Celular em Cardiologia

Conclusões:

1. Método seguro
2. Eficácia experimental estabelecida
3. Efeito definido sobre contratilidade
4. Incremento contrátil limitado e variável
5. Ação difusa, não localizada
6. Via de administração ?
7. Dose(quantidade de células) ?
8. Momento da aplicação ?
9. Efeitos em IC, IAM, DAC ?

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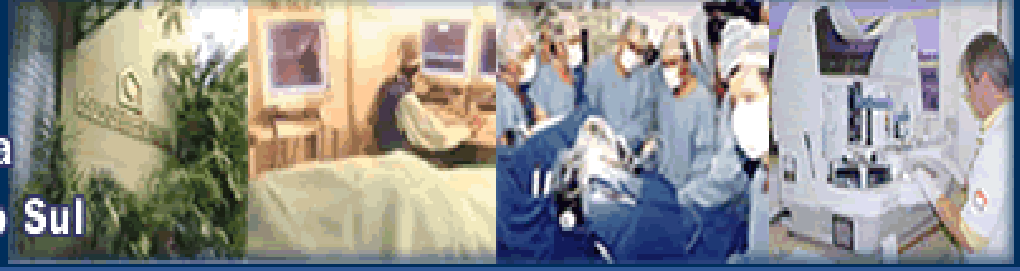

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