

# Heart Failure Improvement After Autologous Bone Marrow Mononuclear Cells Transplantation

J Tuma-Mubarak, MD<sup>1\*</sup>, R Fernandez-Viña, MD<sup>2</sup>, A Carrasco-Yalan, MD<sup>3</sup>, J Castillo, MD<sup>3</sup>, H Rios, MD<sup>3</sup>, C Cruz, MD<sup>1</sup>, A Carrillo, MD<sup>1</sup>, J Ercilla, MD<sup>1</sup>, C Yarleque, MD<sup>1</sup>, J Cunza, MD<sup>1</sup>, and A Patel MD<sup>4</sup>.

For the **TELCECORI HF PERU** Investigators\*(Terapia Celular Corazon Improves Heart Failure)

## Background

Pilot studies suggest that transc coronary transplantation of progenitor cells derived from bone marrow (ABMMC) may improve left ventricular ejection fraction (LVEF) in heart failure patients

## Methods

Eighteen patients were enrolled and completed 1 year follow up. Patients underwent SPECT evaluation, all had ejection fraction  $\leq 35\%$ , 6 patients were allocated to the control group and 12 in Bone Marrow Cells (ABMMC) group, median age 65 years old, all but one were male; all with ischemic cardiomyopathy. All of cohort had NYHA class of III with maximal medical therapy and median basal LEVF was 29.8%. Median number of mononuclear and CD34+ cells infused were  $8.1 \times 10^8$  and  $1.2 \times 10^7$  respectively in a 50 cc delivered retrograde via coronary sinus approach using balloon occlusion over wire for 8 to 10 minutes. No study related adverse events were observed.

## Results

After a median time of 21 days, patients in the ABMMC group had relief of dyspnea symptoms and improvement in functional class. At 1 year, NYHA class improved in 92% of the patients in the ABMMC group by at least 1 class and no improvement in the control group. Mean improvements of LVEF post ABMMC transplantation were 5.4% and 6.67% at rest and stress SPECT respectively. Rest LVEF at baseline and after one-year follow up between the ABMMC and control groups demonstrates significant difference (5.4% vs 1.1%,  $p=0.009$ ), as well as the comparison of change in stress LVEF in both groups (6.6% vs 0.11%,  $p<0.001$ ).

## Conclusions

Infusion of progenitor cells into the coronary veins is safe and feasible in the ischemic HF. It is associated with significant improvement in symptoms, functional capacity and LVEF.

---

From the <sup>1</sup>Department of Interventional Cardiology and Regenerative Medicine, Clinical Ricardo Palma, Clinical Maison de Sante-CENCOR, Lima, Perú; <sup>2</sup>Don Roberto Fernandez Viña Foundation, San Nicolas, Argentina; <sup>3</sup>Instituto de Criopreservación y Terapia Celular, Lima, Perú and <sup>4</sup>University of Pittsburgh Medical Center, Pittsburgh, PA, United States.

## Correspondence

\*Cardiovascular Center and Regenerative Medicine CENCOR Maison de Sante. Gregorio Escobedo 676 of 211 L-11 Lima, PERÚ. [cencor@maisondesante.org.pe](mailto:cencor@maisondesante.org.pe)

Chronic heart failure is common, and its prevalence continues to increase.<sup>1</sup> Ischemic heart disease is the principal cause of heart failure.<sup>2</sup> Although myocardial salvage due to early reperfusion therapy has significantly reduced early mortality rates,<sup>3</sup> postinfarction heart failure resulting from ventricular remodeling remains a problem.<sup>4</sup> One possible approach to reversing postinfarction heart failure is enhancement of the regeneration of cardiac myocytes as well as stimulation of neovascularization within the infarcted area. Initial clinical pilot studies have suggested that transcatheter infusion of progenitor cells is feasible and may beneficially affect postinfarction remodeling processes in patients with acute myocardial infarction.<sup>5-12</sup> However, it is currently unknown whether such a treatment strategy may also be associated with improvements in cardiac function in patients with persistent left ventricular dysfunction due to healed myocardial infarction with established scar formation.

Therefore, in the prospective TELCECORI HF PERU (Terapia Celular Corazon Improves Function in Patients with Heart Failure) trial, we investigated whether percutaneous retrograde sinus technique infusion of autologous bone marrow mononuclear cells (ABMMC) into the coronary veins at least 6 months after myocardial infarction improves global left ventricular function.

## Methods

### Patients

From May 2005 to November 2006, a total of 18 patients who had had a myocardial infarction and ischemic cardiomyopathy were recruited in a multicenter study. Patients between 41 and 81 years of age were eligible for inclusion in the study if they had had a documented myocardial infarction at least more than 6 months before inclusion and had a left ventricular dysfunction  $\leq 35\%$ . None of these patients were candidates for myocardial revascularization surgery neither angioplasty nor resynchronization therapy. Exclusion criteria were the presence of acutely decompensated heart failure with a New York Heart Association (NYHA) class IV, a history of other severe chronic diseases or cancer, or unwillingness to participate. The ethics review board of the Peruvian foundation of regenerative medicine, approved the protocol and the study was conducted in accordance

with the Declaration of Helsinki. Written informed consent was obtained from each patient.

### Study Design

The study consisted in clinical status and Spect evaluation at baseline and 1 year follow up.

The primary end point of the study addresses the safety of ABMMC infusion into the coronary veins. And the secondary end points included the absolute change in global left ventricular ejection fraction (LVEF) as measured by quantitative SPECT at rest and stress evaluation at baseline and 12 months after cell infusion. In addition functional status was assessed by NYHA classification.

### Preparation and Transplantation of Progenitor Cells

For patients assigned to receive ABMMC a median volume of 345 ml of bone marrow aspirate was obtained while the patients were under local anesthesia on the morning of cell-transplantation day. ABMMC were isolated by Hess density-gradient centrifugation, as previously reported.<sup>13</sup> We infused a median number of mononuclear and CD34+ cells  $8.12 \times 10^8$  and  $1.206 \times 10^7$  respectively in a median volume of 50 ml. The total procedure time for implantation was 30 minutes. The right internal jugular vein was cannulated with local anesthesia and place a 7 French sheath, then the coronary veins were catheterized with left amplatz or multipurpose and place a guide 0.035 mm in the interventricular anterior or lateral vein and exchange with the balloon thereafter in a good position, we begin to infuse ABMMC and leave the balloon insufflated for 10 minutes producing stagnation of the flow as previously described.<sup>14-17</sup> (Figure 1, 2)

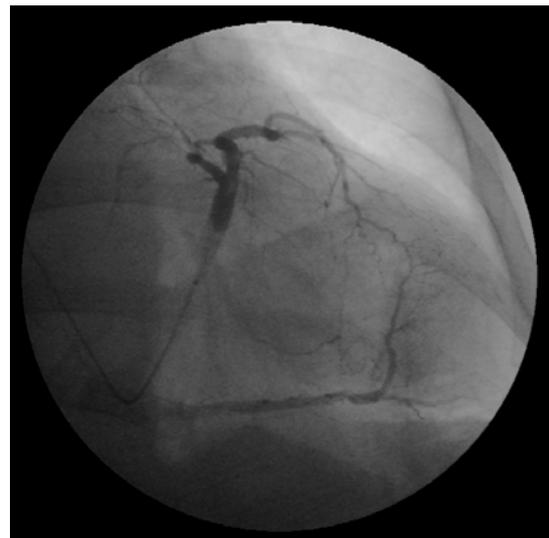
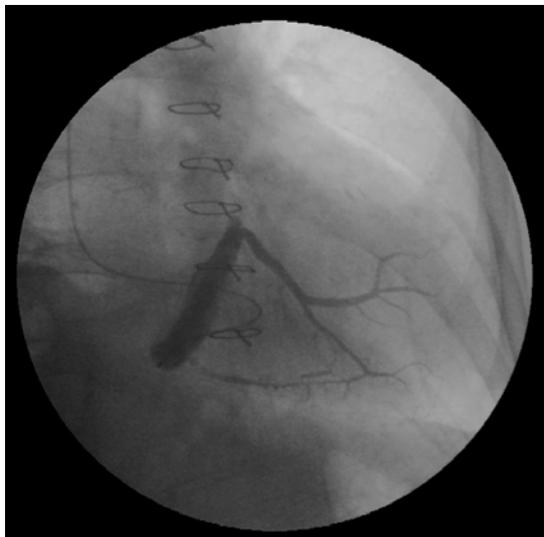


Figure 1. Transplantation of unselected ABMMC into the coronary veins.

**Figure 2. Transplantation of unselected ABMMC into the lateral veins.**



**Evaluation of Safety and Feasibility**

Clinical, laboratory, and safety-related data were prospectively collected. Follow-up visits after 1 month was performed by physicians. Procedural complications were defined as any ventricular arrhythmia, visible thrombus formation or injury of the coronary veins associated with the cell-infusion catheterization procedure. For patients undergoing bone marrow aspiration, potential bleeding complications were assessed. During hospitalization, telemetry was routinely performed for 12 hours after the procedure in all patients.

**Single-photon emission computed tomography Spect-Imaging**

For the SPECT examination, a 1-day rest-stress protocol was used. On the same day, images at rest were obtained 60 minute after the injection (using <sup>99m</sup>Technetium Sestamibi, acquired in gated). Imaging was performed with a double-head SPECT camera as previously described.<sup>18-19</sup> The stress protocol included a symptom limited bicycle exercise test. <sup>99m</sup>Technetium Sestamibi was injected intravenously at peak exercise 85% of the estimated heart rate, which was continued for 2 minute after tracer injection, images was obtained 60 minute after the stress test. In patients unable to perform physical exercise, adenosine (n = 8) was used. Reconstruction yielded long-and short -axis projections perpendicular to the heart axis. The short-axis slices were displayed in polar map format, adjusted for peak myocardial activity (100%).

**Statistical Analysis**

Data are reported as means +/- SDs. Quantitative data were compared using 2 tails Student's test. Categorical data were compared using the chi-square test, a p value 0.05 was considered significant. Statistical analysis was performed using SPSS 14.00.

**Results**

**Baseline Characteristics of the Patients**

A total of 18 patients were enrolled in the study. Of these, 12 patients received ABMMC treatment, and 6 patients in the control group. *Table 1* illustrates that the two groups of patients were well matched.

**Table 1. Baseline characteristics of patients ABMMC and Control Group.**

CHARACTERISTIC	ABMMC (N = 12)	CONTROL GROUP(N=6)	p-value
Age – yr Mean	65 ±14.3	64 ±10	NS
Male sex – N (%)	11 (91.6%)	6 (100%)	NS
Systemic Hypertension - N (%)	9 (75%)	6 (100%)	NS
Hyperlipidemia – N (%)	7 (58.3%)	5 (83.3%)	NS
Diabetes Mellitus - N (%)	4 (33.3%)	2 (33.3%)	NS
Previous myocardial infarction	12 (100%)	6 (100%)	NS
Previous percutaneous coronary intert	5 (41.6%)	4 (66.6%)	NS
Previous coronary artery bypass surge	7 (58.3%)	4 (66.6%)	NS
NYHA III (%)	12 (100%)	6 (100%)	NS
LVEF at Rest – Mean	28.56±6.53	32.2±1.85	NS (p=0.1)
LVEF at Stress – Mean	27.81±6.82	31.71±1.39	NS (p=0.08)

### Effects of ABMMC transplantation

Thus, SPECT-derived assessment of left ventricular function further corroborated the results obtained from the total patient population. Analysis of global left ventricular function revealed that ABMMC treatment significantly increased. The mean ( $\pm$ SD) LVEF post transplantation by SPECT at rest improved from 28.56% to 33.98% in the ABMMC arm ( $p=0.009$ ) with not significant changes in the control group (32.2% to 33.3%). The absolute change in left ventricular ejection

fraction at stress was significantly greater among patients receiving ABMMC (+6.6 percentage points) than among the control group (+0.1 percentage points) ( $p<0.001$ ). The absolute changes in global LVEF from baseline to 12 months differ among the two groups of patients. (Table 2-3)

**Table 2. LVEF at rest and stress in control and ABMMC group.**

<b>REST</b>				<b>STRESS</b>			
Global LVEF (%) Mean $\pm$ SD	CONTROL (N=6)	ABMMC (N=12)	P value	Global LVEF (%) Mean $\pm$ SD	CONTROL (N=6)	ABMMC (N=12)	P value
Baseline	32.2 $\pm$ 1.85	28.56 $\pm$ 6.53	NS	Baseline	31.71 $\pm$ 1.39	27.81 $\pm$ 6.82	NS
1 Year	33.34 $\pm$ 2.59	33.98 $\pm$ 6.03	0.809	1 Year	31.82 $\pm$ 1.06	34.48 $\pm$ 5.50	0.131
Absolute difference	1.14 $\pm$ 1.6	5.42 $\pm$ 4.39	<b>0.009</b>	Absolute difference	0.11 $\pm$ 1.41	6.67 $\pm$ 4.53	<b>&lt;0.001</b>

**Table 3. Summary of ABMMC Group: NYHA and LVEF at Rest and Stress.**

Patient Number	Age	NYHA		REST Left Ventricular Ejection Fraction (%)			STRESS Left Ventricular Ejection Fraction (%)		
		Baseline	1 year	Baseline	1 year	Improvement	Baseline	1 year	Improvement
1	68	3	2	18.5	30.7	<b>12.1</b>	21.3	29.9	<b>8.7</b>
2	68	3	2	15.8	25.0	<b>9.2</b>	15.5	28.9	<b>13.4</b>
3	41	3	2	22.3	24.6	<b>2.3</b>	19.0	26.0	<b>7.1</b>
4	55	3	2	34.8	36.7	<b>2.0</b>	34.4	38.7	<b>4.3</b>
5	81	3	3	31.6	31.9	<b>0.3</b>	31.9	32.6	<b>0.7</b>
6	67	3	2	34.1	35.9	<b>1.8</b>	33.6	38.4	<b>4.8</b>
7	80	3	2	32.6	39.2	<b>6.6</b>	32.6	39.2	<b>6.6</b>
8	69	3	2	30.5	35.8	<b>5.3</b>	29.9	42.6	<b>12.7</b>
9	81	3	2	31.7	33.8	<b>2.1</b>	30.0	39.0	<b>9.1</b>
10	48	3	2	30.8	32.2	<b>1.3</b>	31.6	33.3	<b>1.7</b>
11	67	3	2	35.0	47	<b>12.0</b>	34	42	<b>8.0</b>
12	46	3	2	25.0	35.0	<b>10.0</b>	20	30	<b>10</b>
Mean $\pm$ SD	65.9 $\pm$ 13.68	3 $\pm$ 0.0	2.5 $\pm$ 0.32	28.56 $\pm$ 6.75	33.90 $\pm$ 6.32	<b>5.42 <math>\pm</math>4.36</b>	27.81 $\pm$ 6.68	34.71 $\pm$ 5.71	<b>6.67 <math>\pm</math>4.46</b>

The functional status of the patients, as assessed by NYHA classification, improved significantly in the ABMMC group (from  $3.0 \pm 0.0$  to  $2.08 \pm 0.28$ ,  $P = 0.002$ ) (Table 4)

NYHA Mean $\pm$ SD	CONTROL (N=06)	ABMMC (N=12)
Baseline	3 $\pm$ 0	3 $\pm$ 0
1 Year	3 $\pm$ 0	2.08 $\pm$ 0.28
P value (baseline vs. 1 year)	NS	0.002

**Table 4 (NYHA) improved significantly in ABMMC group**

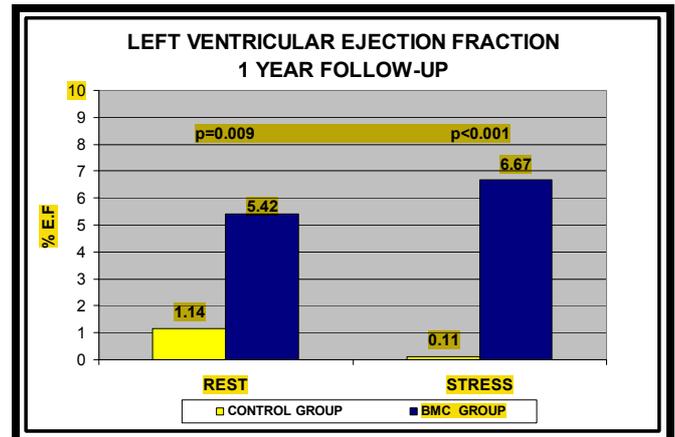
End-Systolic volumen (ESV) and end-Dyastolic volumen (EDV) were evaluated with rest and stress SPECT. Either ESV and EDV do not show any improvements at rest SPECT between the ABMMC and control group; while with the stress SPECT assessment, the ESV did show significant difference between ABMMC and control group ( $-15.4$  ml vs  $0.1$  ml,  $p=0.05$ ). EDV changes with stress SPECT between both groups did not show difference.

#### Procedural Safety and Clinical Outcomes

In 2 of the 12 retrograde progenitor-cells–infusion procedures local dissection of the coronary wall was angiographically visible after inflation of the balloon during cell infusion; in these cases the dissection was not treated and the anticoagulation was reversed with protamine. The further clinical course of these two patients was uneventful.

#### Discussion

Using a prospective and comparative study design, we examined the effects of coronary vein infusion of adult progenitor cells on left ventricular function assessed by SPECT study in patients with chronic ischemic heart disease who had had a myocardial infarction more than 6 months before inclusion. The principal finding of our study is that percutaneous retrograde sinus technique administration of ABMMC is associated with a significant increase in the recovery of left ventricular ejection fraction in patients with left ventricular dysfunction. After 1 year, rest and stress LVEF was significantly higher in the ABMMC group than in the control group. So we evaluated the response of rest and stress LVEF in patients with ABMMC group and control group. Our results demonstrate that infusion of ABMMC into the coronary veins is associated with



**Figure 3. LVEF in the ABMMC group and control group**

significant improvements in rest and stress LVEF evaluation at follow up.

Although resting LVEF improved in only 50 % of patients despite the presence of substantial improvement in functional class, stress LVEF improve in 83%. Therefore, stress LVEF identified additional patients who benefited from cell therapy in terms of global stress function, even though resting function did improve.<sup>20-27</sup> Although previous studies have shown that additional benefits (besides recovery of resting function) may be present after ABMMC, the present study uniquely showed that stress LVEF could improve also in patients without improved resting LVEF.

It has been suggested that, although resting function does not improve, the contractile reserve may increase during stress challenge after revascularization.<sup>28</sup>

However, the mechanisms involved in mediating improved contractile function after progenitor-cell infusion are not well understood. Experimentally, although there is no definitive proof that cardiac myocytes may be regenerated, however angiogenesis was demonstrated in Brazilian heart failure patients, who died of unrelated causes after cellular infusion. The treated area had substantially more blood vessels and other unusual histologic features.<sup>29</sup>

ABMMC were shown to contribute to functional recovery of left ventricular contraction when injected into infarcted hearts and ventricular dysfunction.<sup>12</sup> Both cell types mononuclear and CD34+ were shown to prevent cardiomyocyte apoptosis and reduce the development of myocardial fibrosis and thereby improve cardiac function in heart failure patients.<sup>19,20</sup> Indeed Relief of ischemia by angiogenesis or activation of cardiac stem cell due to paracrine effects may be the possible mechanism responsible for maintaining the contractile

function<sup>30-32</sup>. The current study does not explain the cellular mechanisms associated with the significantly improved left ventricular function in the patients treated with ABMMC. These improvements were observed in the presence of full optimal conventional pharmacologic treatment and lasted at least 12 months. Assessment of resting LV function has been used as the method to evaluate the success of ABMMC transplantation in patients with left ventricular dysfunction and viable myocardium. The findings in the present study showed that dual assessment of rest and stress LVEF may improve the method to detect the benefit of cell infusion, since stress LVEF may improve even in patients without improved resting LVEF. Afridi and Rizello<sup>21,22</sup> showed with dobutamine stress echocardiography, that the wall motion score index at peak stress also improved in patients without improved resting function. Although patients with viable myocardium did not always have improved rest LVEF after revascularization, peak stress LVEF improved, the majority of the improvement in stress wall motion score occurred in patients with evidence of ischemia before revascularization. These observations in the present study suggest that assessment of rest and stress LVEF after ABMMC transplantation may be the ideal end point to evaluate the success of cell infusion. Assessment of LVEF at rest and after exercise may be a more appropriate strategy to evaluate fully the benefit of cell transplantation. The improvement of stress LVEF suggests the presence of a sustained contractile reserve and the absence of significant ischemia. Over the last few decades, the assessment of myocardial perfusion from stress and rest myocardial perfusion SPECT has become central to the management of patients with known or suspected coronary artery disease. More recently, electrocardiography-gated SPECT, with the ability to measure LVEF and ventricular volumes has become a routine part of clinical protocols. Gated SPECT evaluation has been widely confirmed to be accurate and non invasive for delineating and identifying scarred

and viable myocardium. This approved procedure seemed safer for this chronically ill, high- risk patients.<sup>33</sup> The treatment of patients with heart failure has become increasingly important given the growing number of cases and their economic impact on the healthcare system. For these patients the therapeutic options remain limited and the coronary veins provide to be safe in our study, without any major periprocedural events (death, myocardial infarction, ventricular arrhythmias, or pericardial effusion, an underexploited route of access to the myocardium for catheter interventions and the delivery of therapeutic agents. The study population is relatively small. Further randomized studies with more patients are needed to clarify the prognostic implications of these findings. Prospective trials are needed to better characterize the efficacy of ABMMC as a new treatment for heart failure. We conclude in this initial prospective, nonrandomized, study in patients with heart failure that Infusion of progenitor cells into the coronary veins is associated with significant improvement in symptoms, functional capacity and LVEF. Without any clinical evidence of significant harm from the procedure itself. We believe there may be clinical potential for this relatively novel therapy. Further investigation in a larger, randomized trial is warranted.

#### Acknowledgments

We thank Nelsa Gomez, Magaly Aranda, RN, and Micaela Arroyo, RN, for their enthusiastic support and coordination of the study patients; Janet Zacarias for the psychological assessment and support of the patients; Samuel Chirinos, Jorge Rafael, for their outstanding technical support; and, for editorial assistance in the preparation of the manuscript.

## REFERENCES:

1. Dallas: American Heart Association, 2000. Braunwald E. Cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med* 1997; 337:1360-9.
2. Lange RA, Hillis LD. Reperfusion therapy in acute myocardial infarction. *N Engl J Med* 2002;346:954-5.
3. Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. *Circulation* 2000; 101:2981-8.
4. Daniele Torella, Georgina M Ellison, Simón Méndez-Ferrer, Borja Ibanez and Bernardo Nadal-Ginard\* 1 Resident human cardiac stem cells: role in cardiac cellular homeostasis and potential for myocardial regeneration. *Nature clinical practice cardiovascular medicine* march 2006 vol 3 supplement. .
5. Simón Méndez-Ferrer, Georgina M Ellison, Daniele Torella and Bernardo Nadal-Ginard Resident progenitors and bone marrow stem cells in myocardial renewal and repair, *Nature clinical practice cardiovascular medicine* march 2006 vol 3 supplement 1.
6. Strauer BE, Brehm M, Zeus T, et al. Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans *Circulation* 2002; 106:1913-8.
7. Assmus B, Schachinger V, Teupe C, et al. Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI). *Circulation* 2002; 106:3009-17.
8. Britten MB, Abolmaali ND, Assmus B, et al. Infarct remodeling after intracoronary progenitor cell treatment in patients with acute myocardial infarction (TOPCARE-AMI): mechanistic insights from serial contrast-enhanced magnetic resonance imaging. *Circulation* 2003; 108: 2212-8.
9. Wollert KC, Meyer GP, Lotz J, et al. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. *Lancet* 2004; 364:141-8.
10. Schachinger V, Assmus B, Britten MB, 9. et al. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction: final one-year results of the TOPCARE-AMI Trial. *J Am Coll Cardiol* 2004; 44:1690-9.
11. Assmus B, Honold J, Lehmann R, et al. Transcoronary transplantation of progenitor cells and recovery of left ventricular function in patients with chronic ischemic heart disease: results of a randomized, controlled trial. *Circulation* 2004; 110 (Suppl. III):238.
12. Strauer BE, Brehm M, Zeus T, et al. Regeneration of human infarcted heart muscle by intracoronary autologous bone marrow cell transplantation in chronic coronary artery disease: the IACT Study. *J Am Coll Cardiol* 2005; 46:1651–1658.
13. Gerd P. Meyer, MD\*; Kai C. Wollert, MD\*; Joachim Lotz, MD; Eighteen Months' Follow-Up Data from the Randomized, Controlled BOOST (BOne marrOw transfer to enhance ST-elevation infarct regeneration) Trial. (*Circulation*. 2006; 113:1287-1294.)
14. Gensini G, Di Giorgi S and Murad S. The coronary circulation: a roentgenographic study Booth # 91 leventh Annual Convention The American College of Cardiology. May 29,30,31, June 1, 1962 Denver, Colorado.
15. Murad – Netto Simportancia do cateterismo do seio coronário no diagnóstico da insuficiência coronária II Simpósio Nacional sobre aterosclerose coronária. São Paulo, 1973 Editor J. Eduardo M.R. Sousa pg. 63-7.
16. Giordano FJ Retrograde coronary perfusion: a superior route to deliver therapeutics to the JACC 2003; 42:1129-31.
17. Ajay K. Jain, MD, Elliot J. Smith, MD, Martin T. Rothman, FRCP, FACC, FESC . Review: The Coronary Venous System: An Alternative Route of Access to the Myocardium *The Journal of Invasive Cardiology - Volume 18 - Issue 11 (Nov 2006) - November 2006 - Pages: 563 – 568.*
18. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002; 105:539 –542. 17.
19. Borger van der Burg AE, Bax JJ, Boersma E, Pauwels EKJ, van der Wall EE, Schalij MJ. Impact of viability, ischemia, scar tissue and revascularization on outcome after aborted sudden death. *Circulation* 2003; 108:1954 –1959.
20. Bax JJ, Wijns W, Cornel JH, et al. Accuracy of currently available techniques for prediction of functional recovery after revascularization in patients with left ventricular dysfunction due to chronic coronary artery disease: comparison of pooled data. *J Am Coll Cardiol* 1997; 30:1451–60.
21. Afridi I, Qureshi U, Kopelen HA, et al. Serial changes in response of hibernating myocardium to inotropic stimulation after revascularization: a

- dobutamine echocardiographic study. *J Am Coll Cardiol* 1997; 30:1233–40.
22. V. Rizzello, D Poldermans, E Biagini, A F L Schinkel, R van Domburg, A Elhendy, E C Vourvouri, M Bountiokos, A Lombardo, B Krenning, J R T C Roelandt, J J Bax Improvement of stress LVEF rather than rest LVEF after coronary revascularisation in patients with ischaemic cardiomyopathy and viable myocardium *Heart* 2005.
  23. Cuocolo A, Petretta M, Nicolai E, et al. Successful coronary revascularization improves prognosis in patients with previous myocardial infarction and evidence of viable myocardium at thallium-201 imaging. *Eur J Nucl Med* 1998; 25:60–8.
  24. Ragosta M, Beller GA, Watson DD, et al. Quantitative planar redistribution 201Tl imaging in detection of myocardial viability and prediction of improvement in left ventricular function after coronary bypass surgery in patients with severely depressed left ventricular function. *Circulation* 1993; 87:1630–41.
  25. Pagano D, Bonser RS, Townend JN, et al. Predictive value of dobutamine echocardiography and positron emission tomography in identifying hibernating myocardium in patients with postischaemic heart failure. *Heart* 1998; 79:281–8.
  26. Elhendy A, Cornel JH, van Domburg RT, et al. Effect of coronary artery bypass surgery on myocardial perfusion and ejection fraction response to inotropic stimulation in patients without improvement in resting ejection fraction. *Am J Cardiol* 2000; 86:490–4.
  27. Rocchi G, Poldermans D, Bax JJ, et al. Usefulness of the ejection fraction response to dobutamine infusion in predicting functional recovery after coronary artery bypass grafting in patients with left ventricular dysfunction. *Am J Cardiol* 2000; 85:1440–4.
  28. Kaul S. There may be more to myocardial viability than meets the eye. *Circulation* 1995; 92:2790–3.
  29. Hans F.R. Dohmann, MD\*; Emerson C. Perin, MD, PhD\*; Christina M. Takiya, MD, PhD; Transendocardial Autologous Bone Marrow Mononuclear Cell Injection in Ischemic Heart Failure Postmortem Anatomicopathologic and Immunohistochemical Findings, (*Circulation*. 2005; 112:521-526.)
  30. Orlic D, Kajstura J, Chimenti S, et al. Bone marrow cells regenerate infarcted myocardium. *Nature* 2001; 410:701-5.
  31. Kocher AA, Schuster MD, Szabolcs MJ, et al. Neovascularization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodeling and improves cardiac function. *Nat Med* 2001; 7:430-6.
  32. Nadal-Ginard B et al. (2003) A matter of life and death: cardiac myocyte apoptosis and regeneration. *J Clin Invest* 111: 1457–1459
  33. Aiden Abidov MD, PhD, Guido Germano, PhD, Rory Hachamovitch, MD, MSc, Daniel S Berman, MD Gated SPECT in assessment of regional and global left ventricular function; Major tool of modern nuclear imaging . *Journal of Nuclear Cardiology* 2006;13:261-79