BUILDING ENDOVASCULAR SYNERGIES

MEET 2008

MULTIDISCIPLINARY EUROPEAN ENDOVASCULAR THERAPY

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Cannes, French Riviera
June 26-29

- **Treatment with Implant and Cellular Therapy in Patients with Acute and Chronical Myocardial Infarction in Argentina (South America)**
- **ANGIOGENESIS AND MYOGENESIS**

Prof. Dr. Fernández Viña Roberto J. MD (1,2,3,4,5,6),
Fundación Don Roberto Fernández Viña Argentina (1),
Clínica San Nicolás B.A Arg. (2),
Universidad Maimonides of Buenos Aires Argentina. (3),
Intitulo de Crianças y Corazón de Río de Janeiro Brasil.(4),
Universidad Fluminense de Rió de Janeiro Brasil.,(5)
Honorary Professor of University of Beiging China

- *FIRST FIVE YEARS FOLLOW UP OF FIRST GROUP OF SOUTH AMERICANS PATIENTS WITH REPAIRED OF* **ACUTE MYOCARDIAL INFARCTION** *BY AUTOLOGOUS INTRACORONARY BONE MARROW* **STEM CELLS IMPLANT.**
- *(THE IMPROVEMENT OF EYECTION FRACTION RECOVERED WAS MAINTAINED AFTER FIVE YEARS)*

Main Researchs

- Fernández Viña Roberto J. (1,2,3,4),
- Andrin Oberdan (1,2),
- Saslavsky Jorge (2,) Vrsalovic Francisco (1),
- Camozzi Liliana(1)
- Fernández Viña R. Federico(1),
- D´Adamo Carla(1,2),
- Muttis Néstor(2),
- Murad Neto Stans(4,5),
- Merlo Isadora(2),
- Tuma Jorge (6),
- Fernández Viña Marcelo (7).
- Fernandez Viña Federico (1)
- Ferreira Da Silva Janaina (1)

Afiliations:

•Fundación Don Roberto Fernández Viña Argentina (1),
•Clínica San Nicolás B.A Arg. (2),
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• Universidad Fluminense de Rió de Janeiro Br.,(5),
•Clínica San Felipe Lima Perú (6),
•MD Anderson Center Texas Houston USA(7)

República Argentina


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- **Ethics Committee:**

- **President: Diputate Dr Ismael Passaglia Md (Ex Minister of Health of Buenos Aires.-**
- **Dr Alberto Viviani.-**
- **Mr Pedro Camozzi.-**
- **Sara Bo (Pharmacist) .-**
- **Mons Ramon Angeles Fernandez (Arquidiosesis Santo Domingo Dominican Rep.)**
- **Notary Jose Servíni.-**
- **Dr. Manuel Herrera Md (Forensic).-**
- **Maria Inês Marino.-**
-

- **Scientific committee:**
- **President: Dr Federico Foresi Md: (internal medicine)**
- **Dr Javier Herrera Md: (Surgeon, experimental surgery)**
- **Dr Carla D'Adamo Md: (clinician)**
- **Dr Danilo Petroni Md (Cardiolgist Clinician/ Echocardiography)**
-

- **External Consultants:**
- **Prof Stans Murad-Netto**: Director of the Institute of Pos Graduação Medica do Rio de Janeiro, Professor of Cardiology of lá Federal Universidade of Rio de Janeiro, Fellow of American College of Cardiology .
- **Prof Miguel Lucas Angel**: Ex- President of the School of Cardiovascular Surgeons and Head Publisher of the Magazine of that organization professor of the University of Salvador BA.-
- **Prof DaeHyun Hwang,** M.D: Hangang Sacred Heart Hospital, Hallym University, Seoul, Korea.-
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- UCLA , USA.-
- **Prof Juan Carlos Chasques:** Head of Service of Cardiovascular Surgery transplants smd implants of the George Pompidou Hospital of Paris,France.-
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- **Dra. Diana Dlugovitzky:** Docente Adscripta Cátedra de Inmunogia de la Facultad de Medicina de Rosario
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- **Dr Gustavo Moviglia:** Presidente y Director Medico e Investigador Principal de Fundacion Regina Mater Buenos Aires Argentina
- **Dr Carlos Gaeta.** Servicio de Cirugía de Hospital Rivadavia de Buenos Aires. Miembro de la Asociación Médica Argentina. Fundacion Regina Mater. Buenos Aires. Argentina
- **Dr. Rogério de Mouras.** Instituto das Crianças de Rio de Janeiro (Brasil).
- **Dr. Roberto M. Serrano:** Medico Cardiólogo Universitário (Universidad del Salvador de Buenos Aires), Clinica Medica , Secretario General de la Federacion Medica de la Capital Federal (Argentina)
- **Mrs. Sonia Cooper:** President, Children With Diabetes Foundation Colorado USA
- University of Colorado Health Sciences Center Barbara Davis Center for
- Childhood Diabetes –Colorado – USA

- **Adhesion to: Ethical principles for the medical investigations in human beings.**
- **(HELSINKI's DECLARA-TION OF THE WORLD MEDICAL ASSOCIATION)**

PROMETEUS

The first history of tissue regeneration

Prometeus robered the Olimpus' Sacred Fire and he was discovered, so the Father God Zeus condemned him to be fixed by chains in a mountain and each morning his liver would be eaten by an Eagle and it would be regenerated in the nights, that it would be eaten all the mornings diuring every days of the rest of Prometeus' life.

ANIMALS EXPERIENCIES With Stems cells in heart

- **Mobilized bone marrow cells repair the infarcted heart, improving function and survival**

- **Donald Orlic*, Jan Kajstura , Stefano Chimenti , Federica Limana , Igor Jakoniuk , Federico Quaini , Bernardo Nadal-Ginard , David M. Bodine*, Annarosa Leri , Piero Anversa ,**
- **Cardiovascular Research Institute, Department of Medicine, New York Medical College, Valhalla, NY 10595; and * Hematopoiesis Section, Genetics and Molecular Biology Branch, National Human Genome Research Institute, National Institute of Health, Bethesda, MD 20892**

- **Edited by Eugene Braunwald, Partners HealthCare System, Inc., Boston, MA, and approved June 29, 2001 (received for review April 11, 2001)**

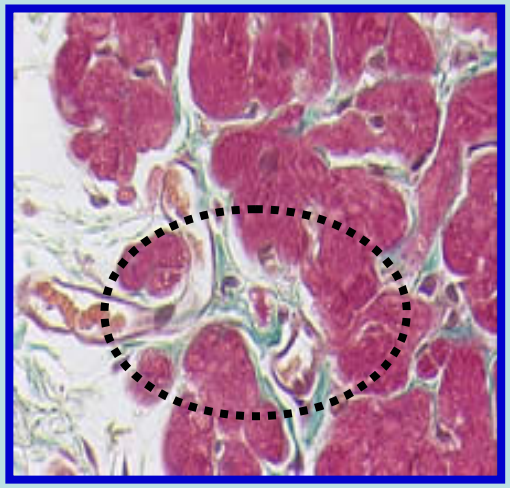
Repair of Infarcted Myocardium by Autologous Intracoronary Mononuclear Bone Marrow Cell Transplantation in Humans

Bodo E. Strauer, MD; Michael Brehm, MD; Tobias Zeus, MD; Matthias Köstering, MD; Anna Hernandez, PhD; Rüdiger V. Sorg, PhD; Gesine Kögler, PhD; Peter Wernet, MD

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

2002
CIRCULATION

Bone marrow stem cells can produce healthy heart muscle and blood vessels



HUMAN EXPERIENCIES

Fundación
Don Roberto
Fernandez Viña

Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI)
Circulation 2003;106:3009-3017
Authors:
B. Assmus

Randomized-Controlled Clinical Trial Of Intracoronary Autologous Bone Marrow Cell Transplantation Post Myocardial Infarction
Associated Meeting: AHA 2003
Reported By: Hani Jneid, MD

2003

1First Reported Case in Argentina of Repair of Infarcted Myocardium by Autologous Intracoronary Bone Marrow Cell Transfusion in a Young Woman: Early Improvement of Ventricular Function and Ischemia
2ANGIOGENESIS: Trans (Coronary) Venous Implantation Of Stems Cells In Chronic Coronary Disease
3Trans (Coronary) LIMA Implantation of Stems Cells in Chronic Coronary Disease

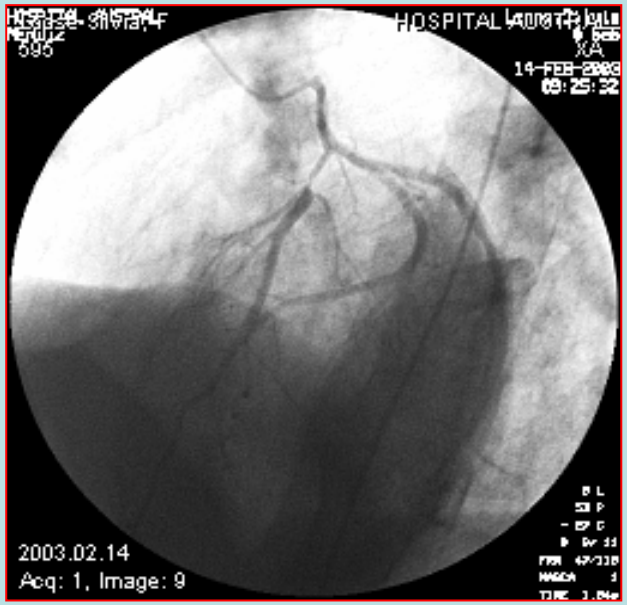
First Reported Case from Argentina of Implant and Cellular Therapy in Myocardial Infarction (TECELCOR Study), TErapia CELular CORazón Argentina

AUTHOR: Fernández Viña Roberto (1)

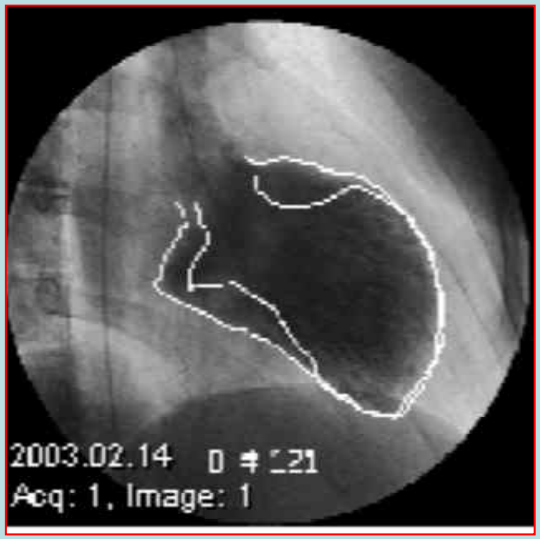
Coauthors: Saslavsky Jorge (1), Andrin Oberdan (1), Vrsalovic Francisco (1), Geffner Luis (2), Camozzi Liliana (1-4), Pinto Andrés (1), Troncoso Mercedes (1), Guilmen Juan (1), García Lorena (1), Dlugovitzky Diana (5), Diez Juan (6), Carla D Ádamo (1-2) Benetti Federico (2), Fernández Viña Marcelo Aníbal (3)

AFFILIATIONS (1) Don Roberto Fernández Viña Foundation Argentina, (2) Benetti Foundation Argentina, (1-2) Centro Cardiovascular San Nicolás; (1-4) Reproductive Bioq. Inmunologic SAEGRE, Arg; (5) Investing. Pal FAC. MEDICINE Rosario Arg.; (6) FAC. MEDICINA Rosario; (3) Professor Dep. of Laboratory Medicine MD Anderson Cancer Center Univ. of Texas, Houston, TX, U.S.A.

Repair of Infarcted Myocardium by Autologous Intracoronary Mononuclear Bone Marrow Cell Transplantation in a young women

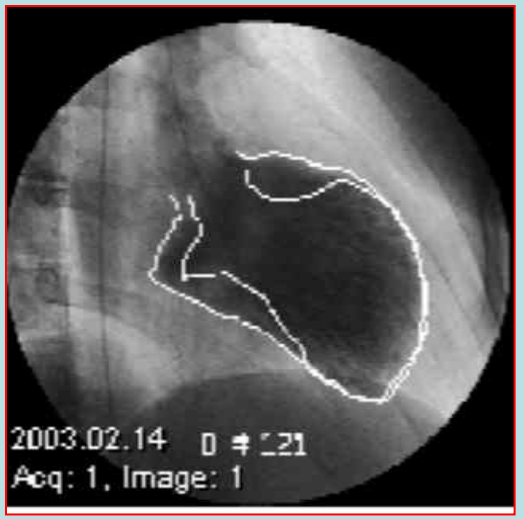


First Reported Case from Argentina



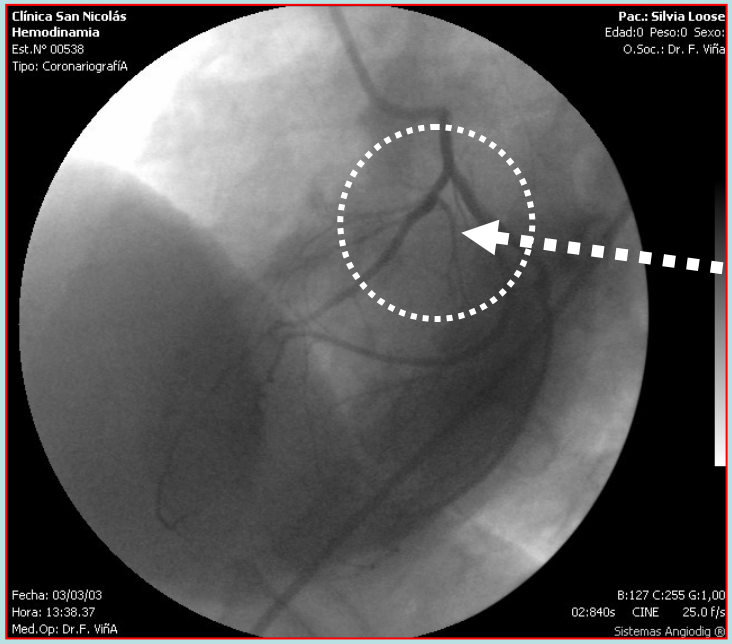
tctmd

April 7, 2003



Fundación Don Roberto Fernandez Viña

PREVIOUS STUDIES



CORONAY SPASM

Fundación Don Roberto Fernandez Viña

Discussion: ¿what can we offer to the patient to change the prognosis?

We proposed to the patient to be subjected to an *Stems Cells Implants*, to attempt *Angiogenesis and Miogenesis* by Intracoronary way.

The patient accepted the treatment previous consented informed.

Type Cells to be implanted:

Two forms of cellular material exist to implant:

a) Whole Bone Marrow

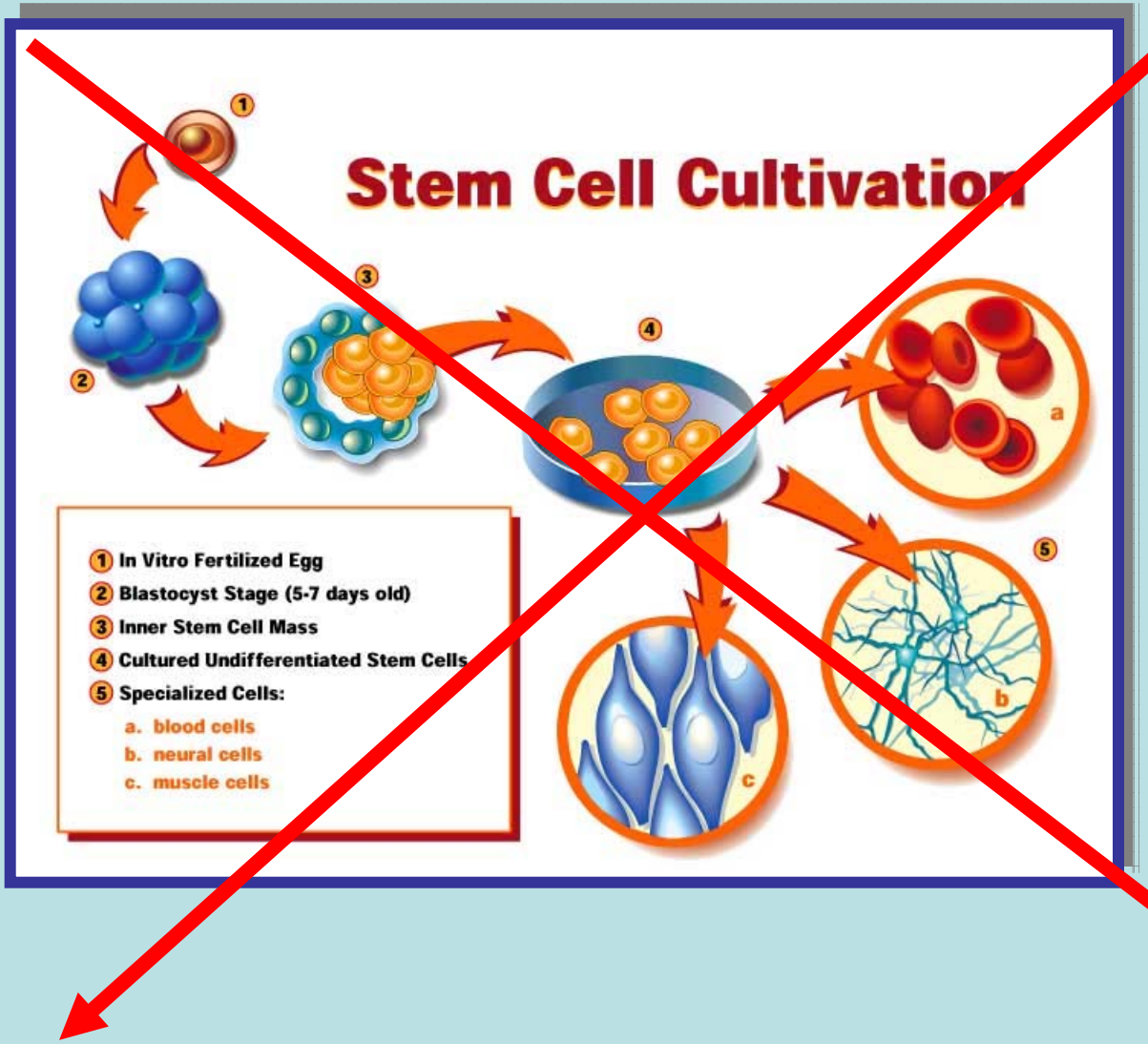
b) Progenitors Cells or Monouclears Cells CD34 (+), CD38 (-) , A113(+) which would be the true Stems cells

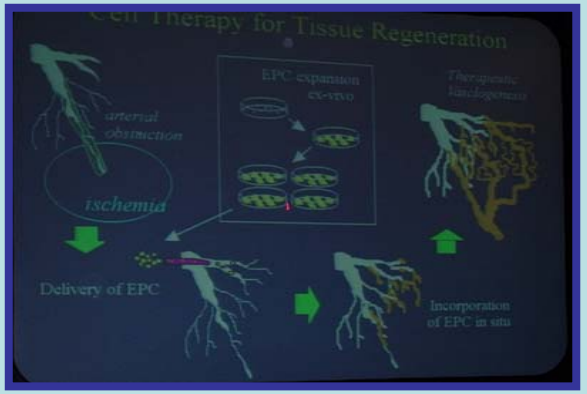
In our service we decide to opt for the "pure" separate cells of the entirety Bone Marrow for several reasons:

1) We preferred implant cells that have demonstrated their transformation capacity and lodging selectively ("homming").

2) To be able to inject bigger quantity of cellular material because it would be impossible to inject great quantity of Whole Marrow with great number of mononuclears cells with membrane markers like those before mentioned,

3) To avoid collaterals effects of other present cells in the bone marrow like for example platelets that could favor the coronary thrombosis





Great cost for Argentina

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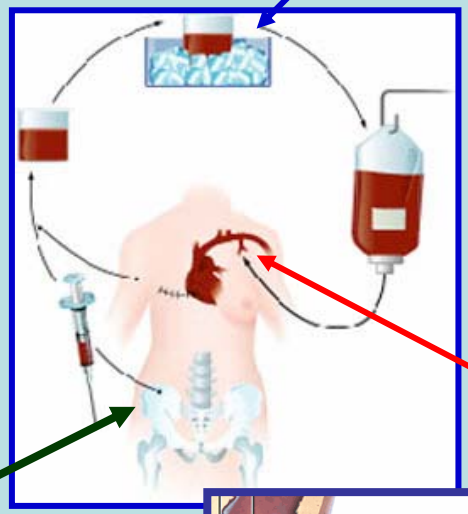
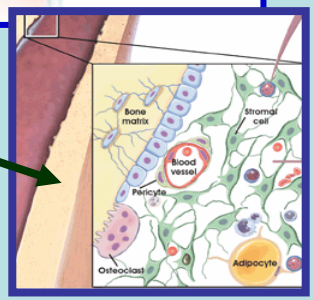
Fernandez Viña

36 mg de Acetil Salicilato de Lisina to aviod agregation platelets was adjunt

The cellular suspension of rooted cells was processed ulteriorly to obtain an enrichment in mononuclears cells for centrifugation in density of gradient being obtained a satisfactory recount This prosecution was made in sterile form and a quantification of the positive cells was made for the marker of cellular surface CD34(+), CD 38(-)





Procedure : was made a punction of bony marrow of the iliac crest
A sample of 500cc of blood was extracted with general anesthetizes

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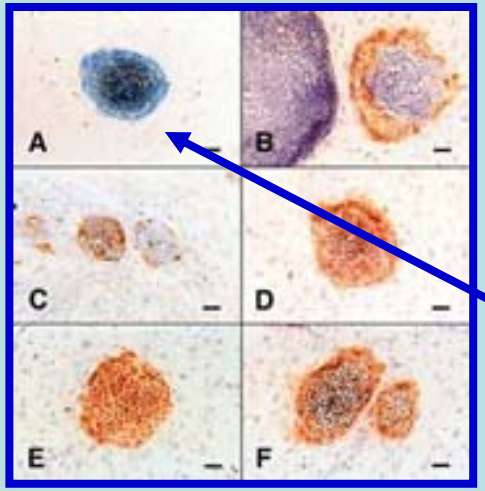
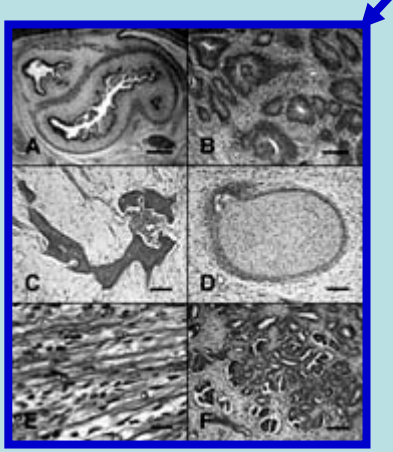
Mononuclear Bone Marrow Cell isolation

Stems Cells Procedure Isolation



The average of Mononuclears Cells obtained was 569 x 10 p6, the average of cells with CD 34 (+)marked was 22,5 x 10p6 and the average of mononuclears cells with CD34(+) & CD38(-) was 3,07 x 10p6.



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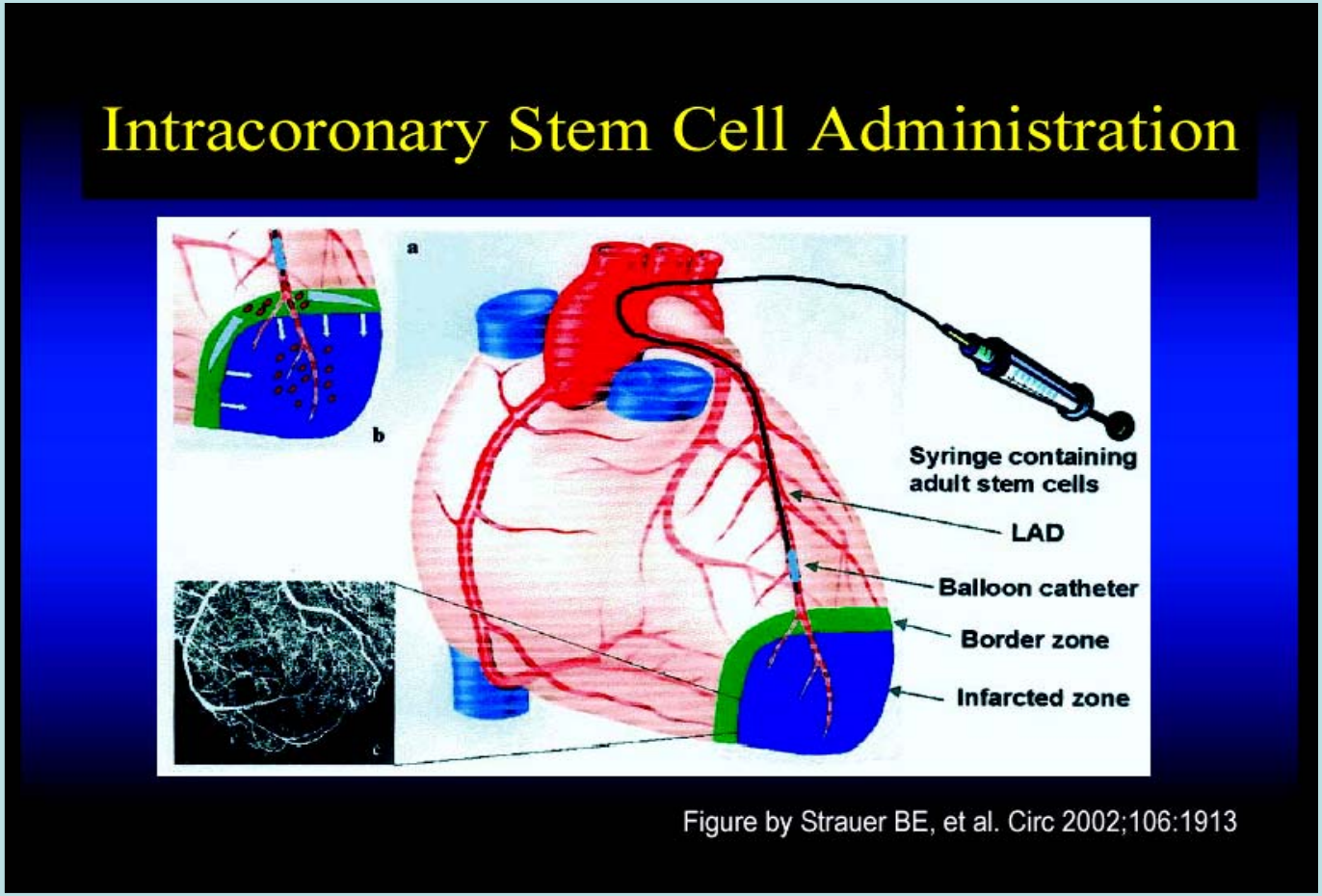
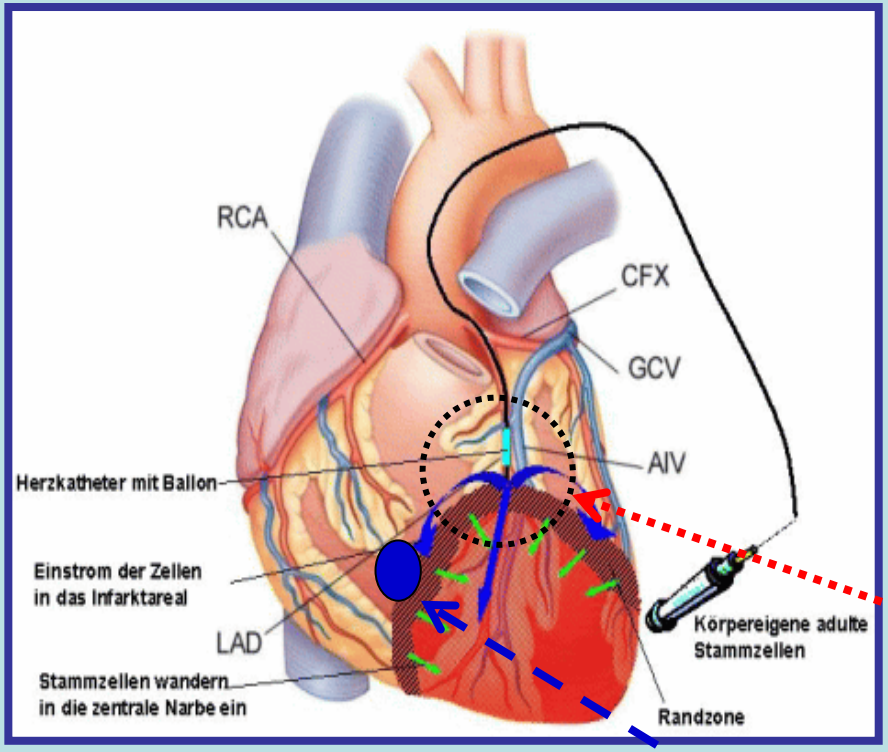
Implant way

The implants way was through the LAD, with occlusion of the coronary artery with a balloon during the implants and with occlusion of the corresponding coronary vein or of the Coronary Sinus with another balloon staying the vein occluded 10 minutes, with the objective to cause Stagnation of the coronary flow during the implants.

Repair of Infarcted Myocardium by Autologous Intracoronary Mononuclear Bone Marrow Cell Transplantation in Humans

Bodo E. Strauer, MD et als



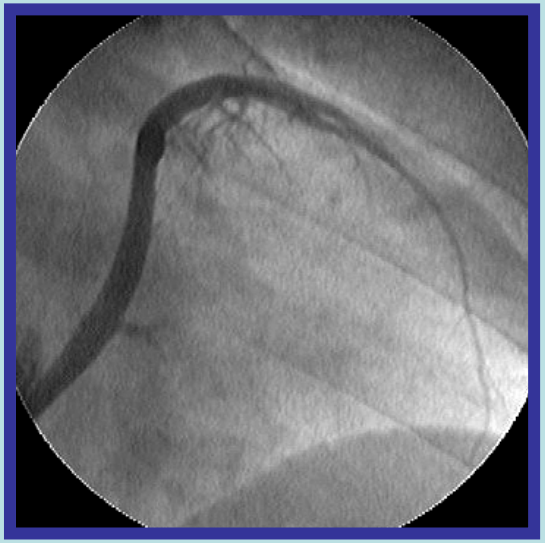


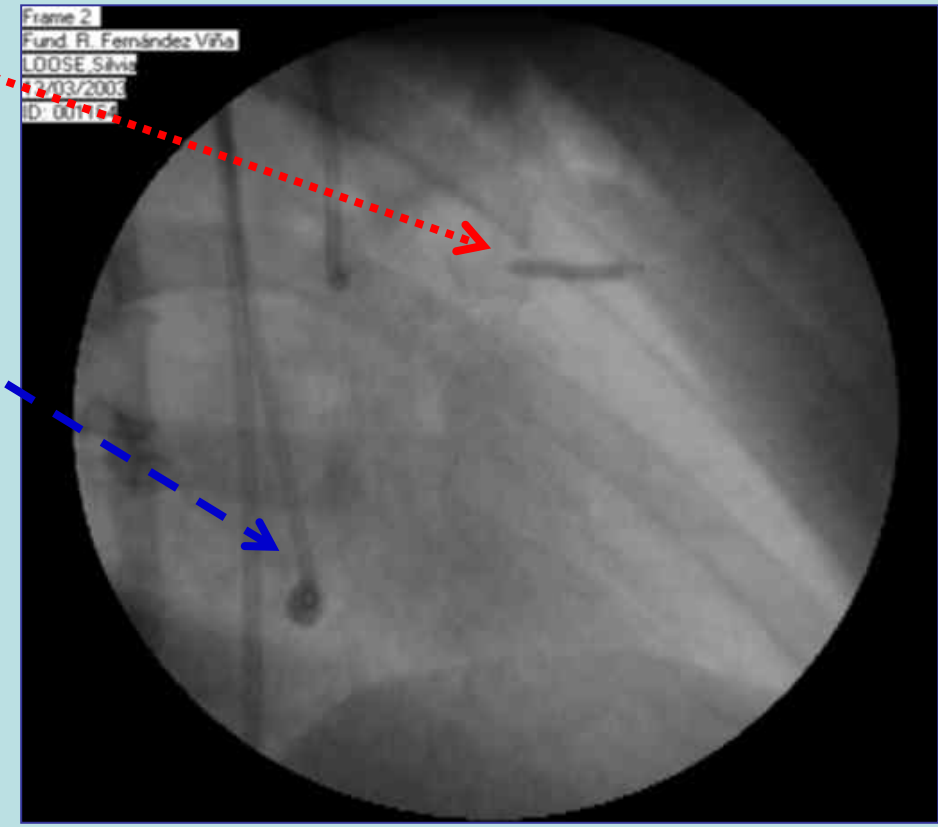
Stagnation of coronary flow in

STEMS CELLS implant

IN

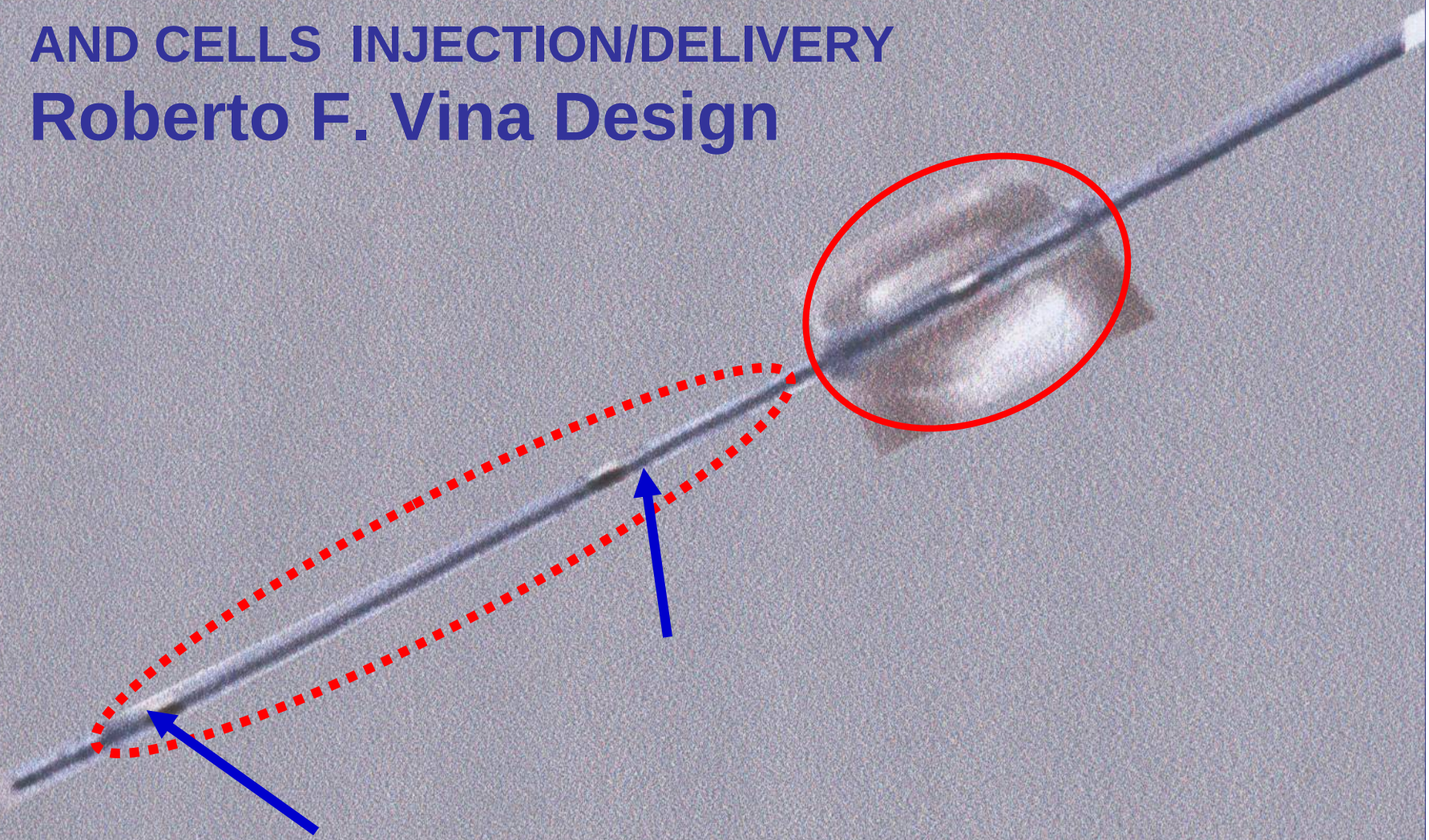
MYOCARDIAL INFARCTION





NAOMI CATHETHER FOR DRUG-GENES AND CELLS INJECTION/DELIVERY

Roberto F. Vina Design



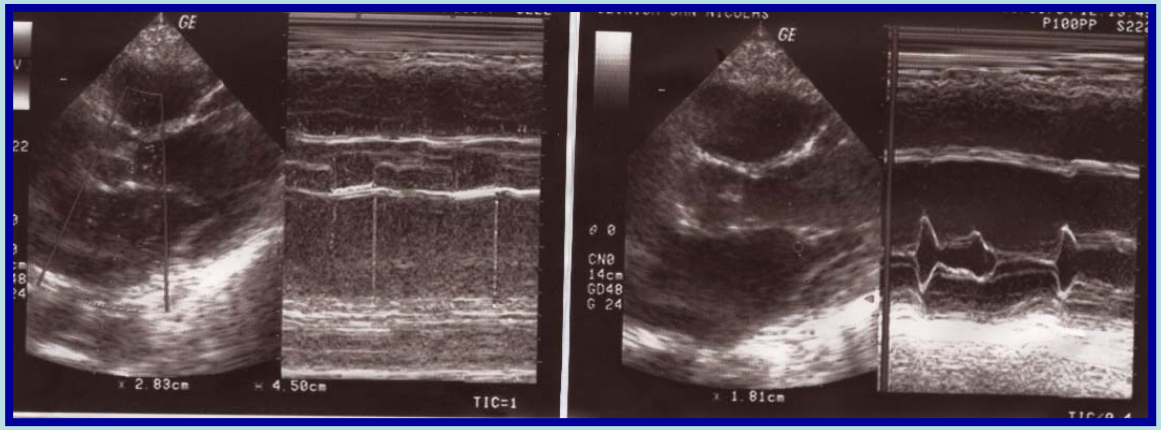
Objetives: Increase Cell Retention

Delivery	%
Anterograde Catheter	**5**
Retrograde Catheter	**5**
Retrograde Catheter - Injection	**15**
Endocardial Catheter - Injection	**20%**
Epicardial Injection - Beating Heart	**30%**
Epicardial Injection - Arrested Heart	**40-50%**

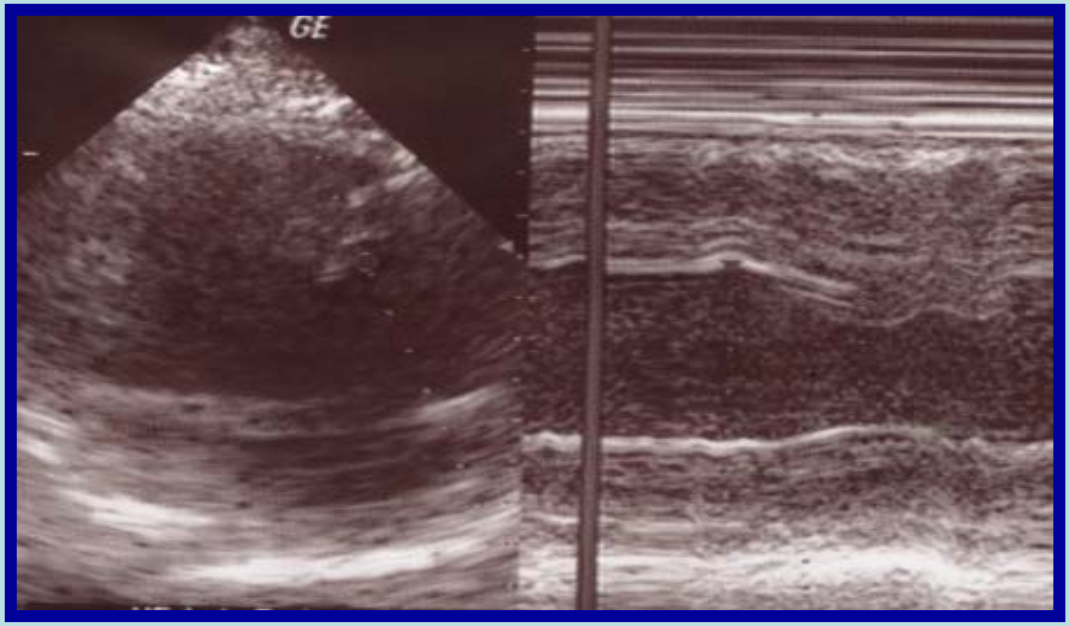
(Early Evolution)

- **E.C.G Appearing little R wave V5,V6.)**
- **Echocardiogram :Improvement of contractility in Anterior and septal walls and improvement of 52% of EF**
- ***SPECT :* <NOT RESIDUAL PERI-NECROTIC AREA AND REDUCTION OF NECROITIC AREA**

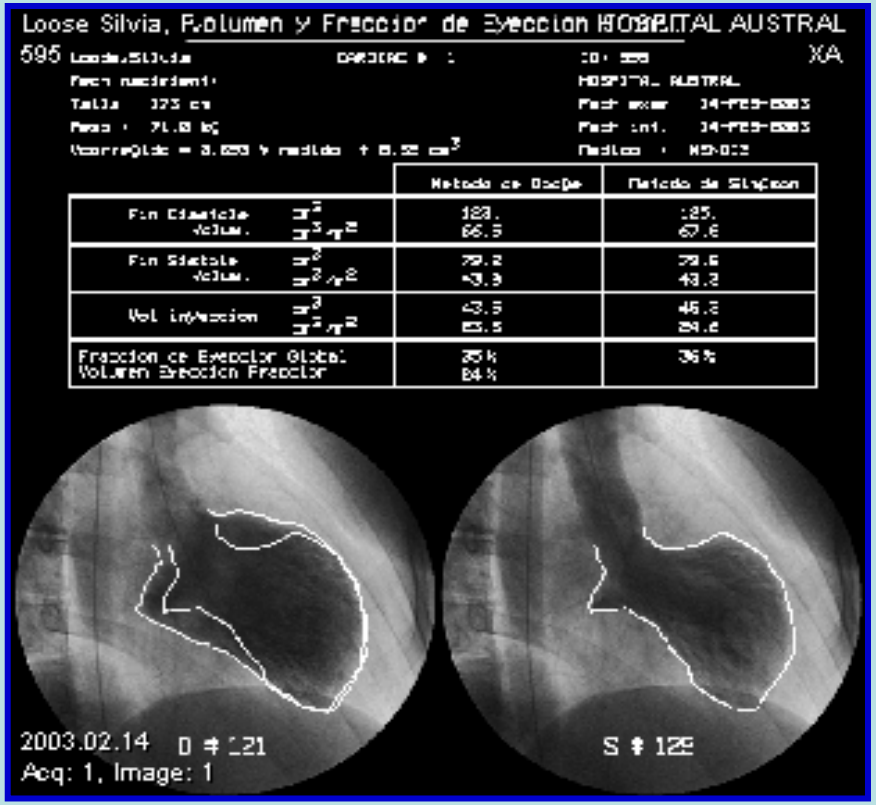
Echocardiogram pre implant



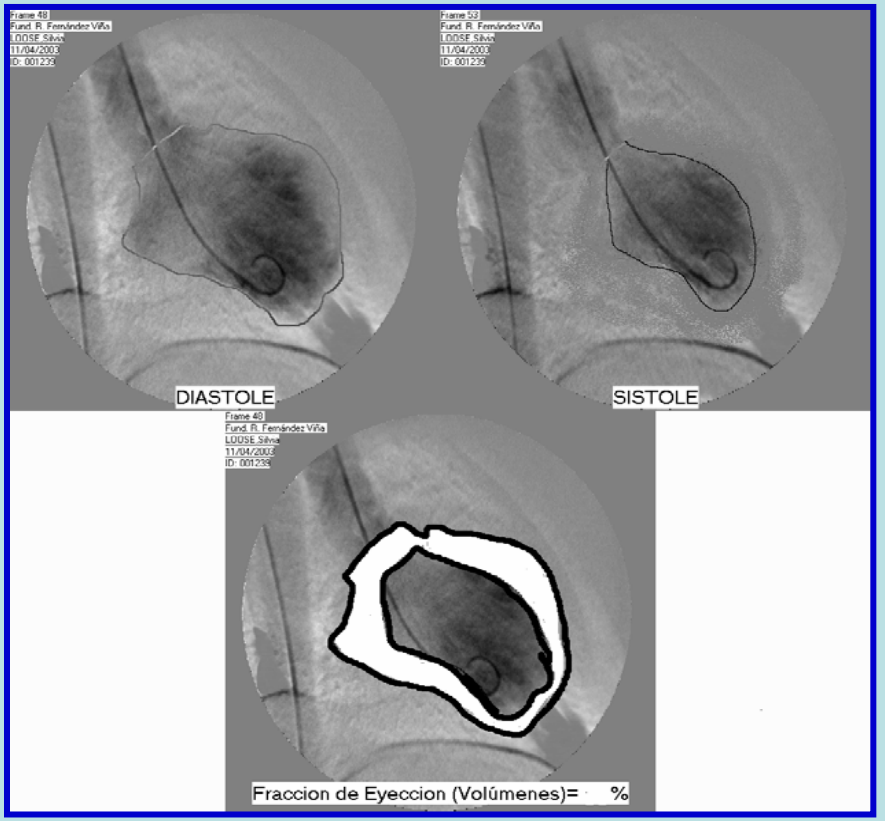
Echocardiogram) post 90 days implant (same patient)



PRE IMPLANT

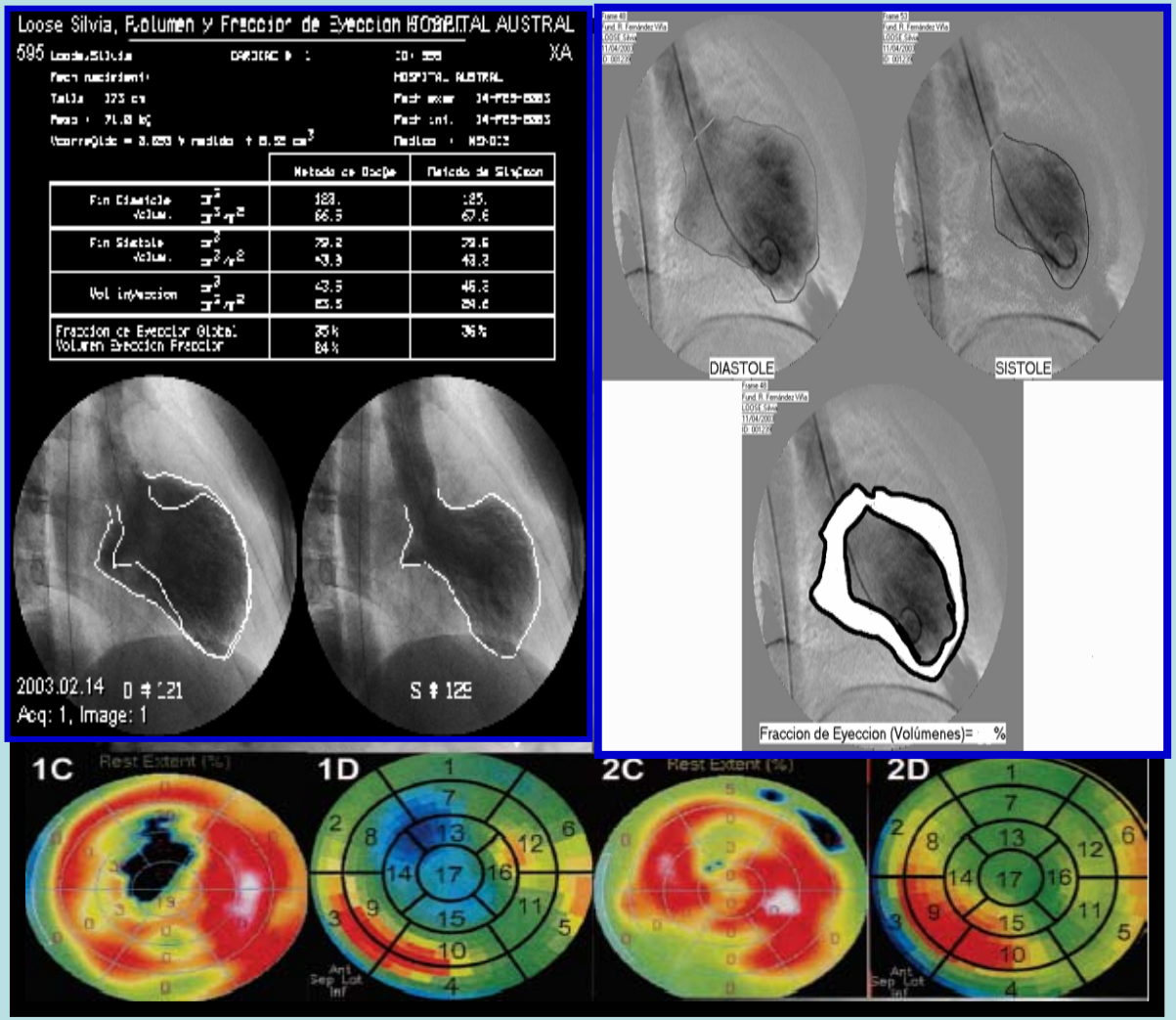


POST IMPLANT



Follow up: 450 days without symptoms with out dysnea neither angina and walk 40 blocks diary asymtomatic

SPECT <NOT RESIDUAL PERI-NECROTIC AREA AND REDUCTION OF NECROITIC AREA



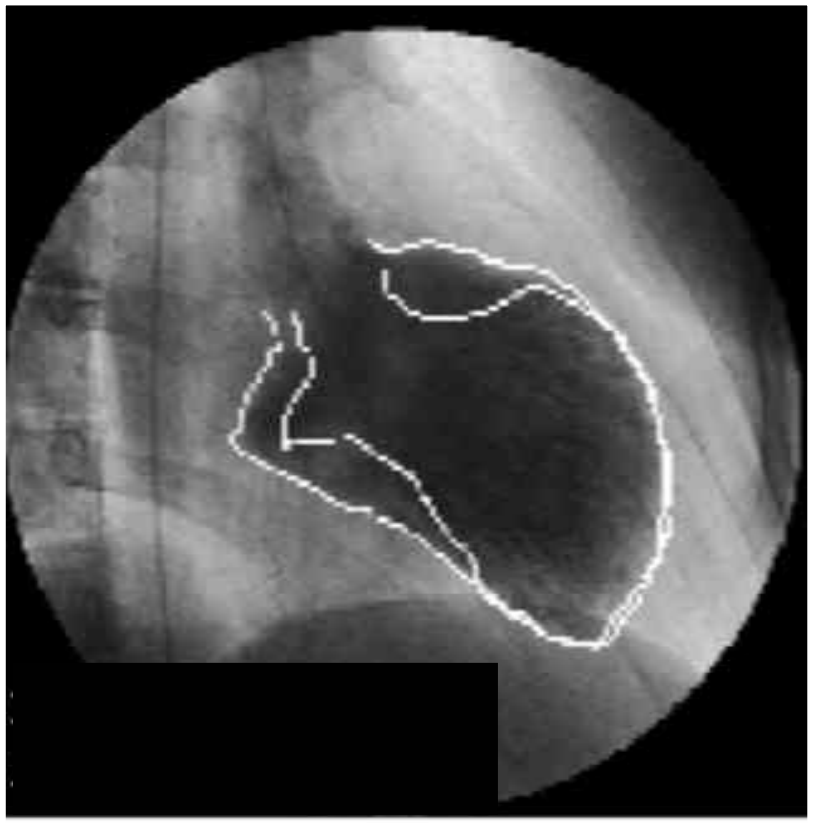
- ***TECELCOR (TErapia CELular CORazón)***

- **Acute Myocardial Infarction Repair with intracoronary implant of Autologous Stem cells (AAMSC)**

Authors: Roberto Fernández Viña MD , et al.

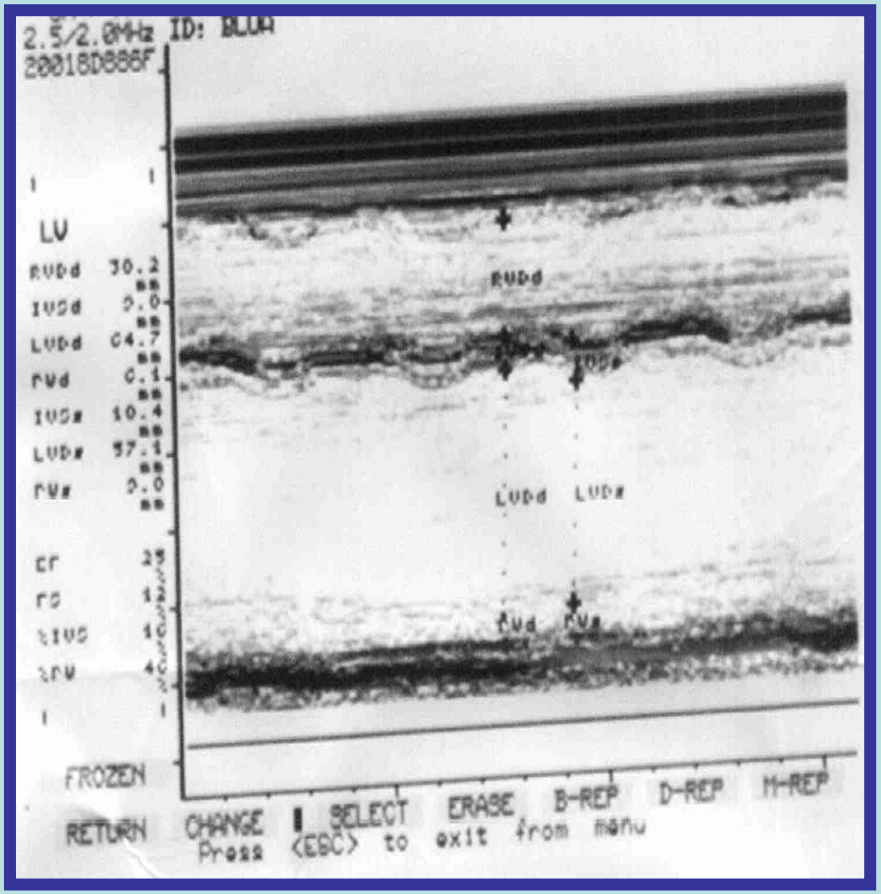
Selections Patients

- Ejection Fraction.VI. Between 21% to 32 %.
- **All the patients had the LAD with total occlusion and they had not another coronary obstruction. PTCA were successful in all the cases**



Selections Patients

In all the patients were made rest echocardiograms, the FE founded oscillated between 19% and 32%, all patients had severe septal akynesis , lost of the septal engrossments.



- (PTCA) con Stenting
- Localization: Anterior Heart Wall Infarction
- Treated Vessel : L.A.D ocludded
- Delay to Implant……. 7 to 10 days
- Way of Implant L.A.D.
- Sinus Coronary Veined Oclussion ……. 100%
- Mortality and Morbilidity ….0% (Aceppted by ETC)

Implant and Cellular Therapy in Acute Myocardial Infarction

IT WERE INCLUDED

- **At first 17pts… then 32 patients that suffered AMI (STCG)**
- **treated with primary PTCA with Stents.**

- **M.I. with more than Six (6) hours of Evolution and**
- **The Ventriculography Ejection Fraction (EF) oscillated between 21 and 32%.**

Control Group Patients **(26)** **that suffered Myocardial infarction with only vessel occlusion (LAD) and whose were treated only with Ptca and stenting and not received Stems cells implantation**

Fraction Ejection of this group of patients between 20 to 34%

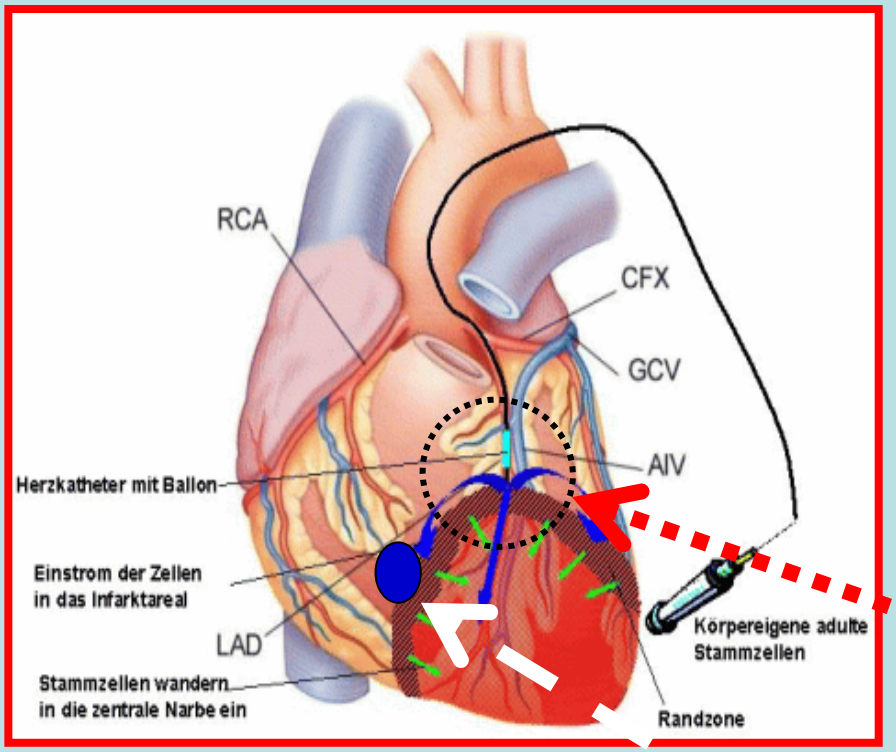
- (SC.Group)
- Stem cell implant
- Follow up

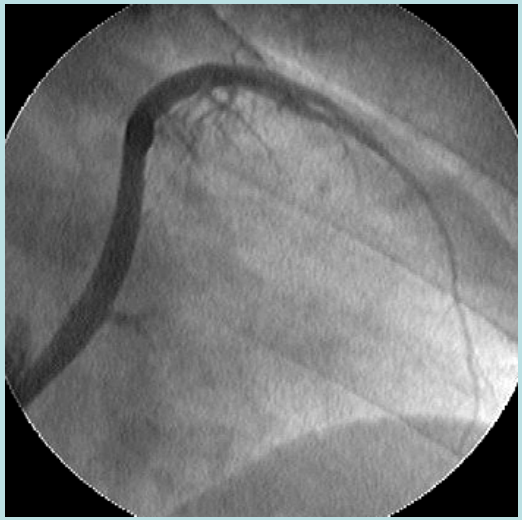
Stagnation of coronary flow in

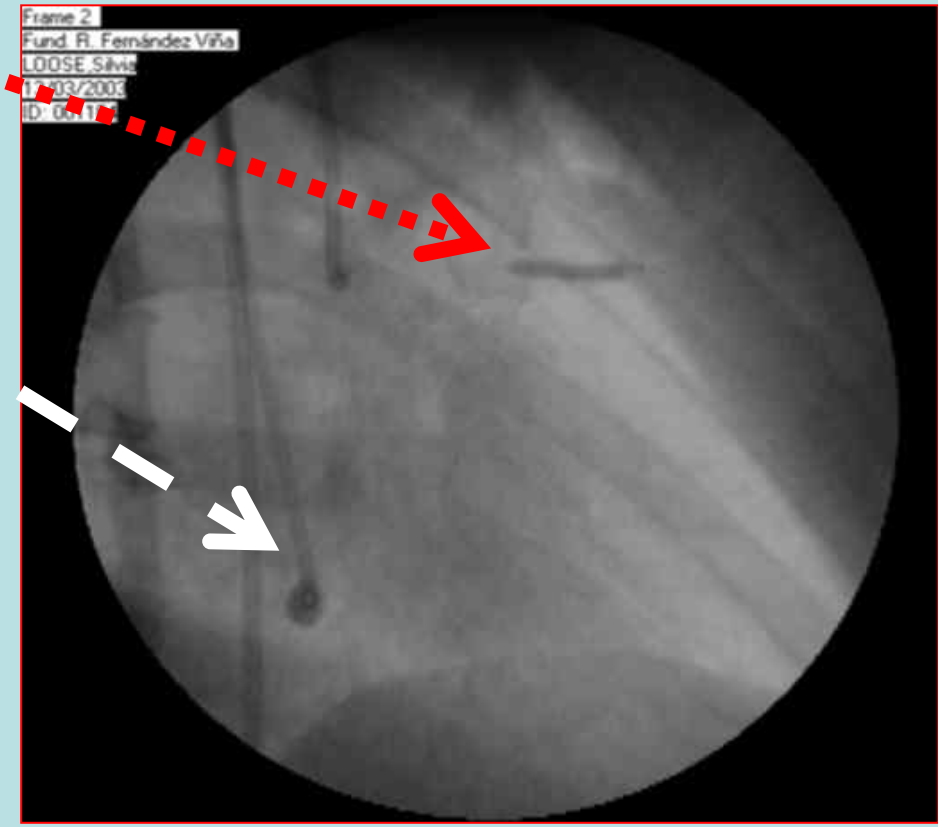
STEMS CELLS implant

IN

MYOCARDIAL INFARCTION







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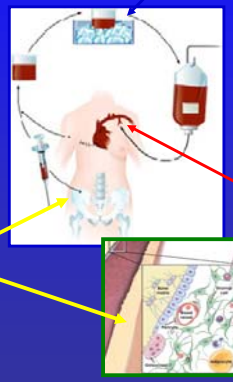

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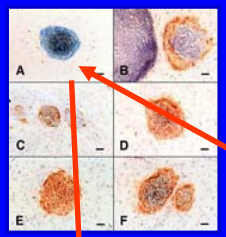
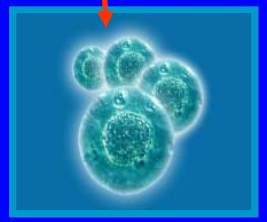
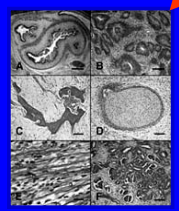
Mononuclear Bone Marrow Cell isolation

Stems Cells Procedure Isolation



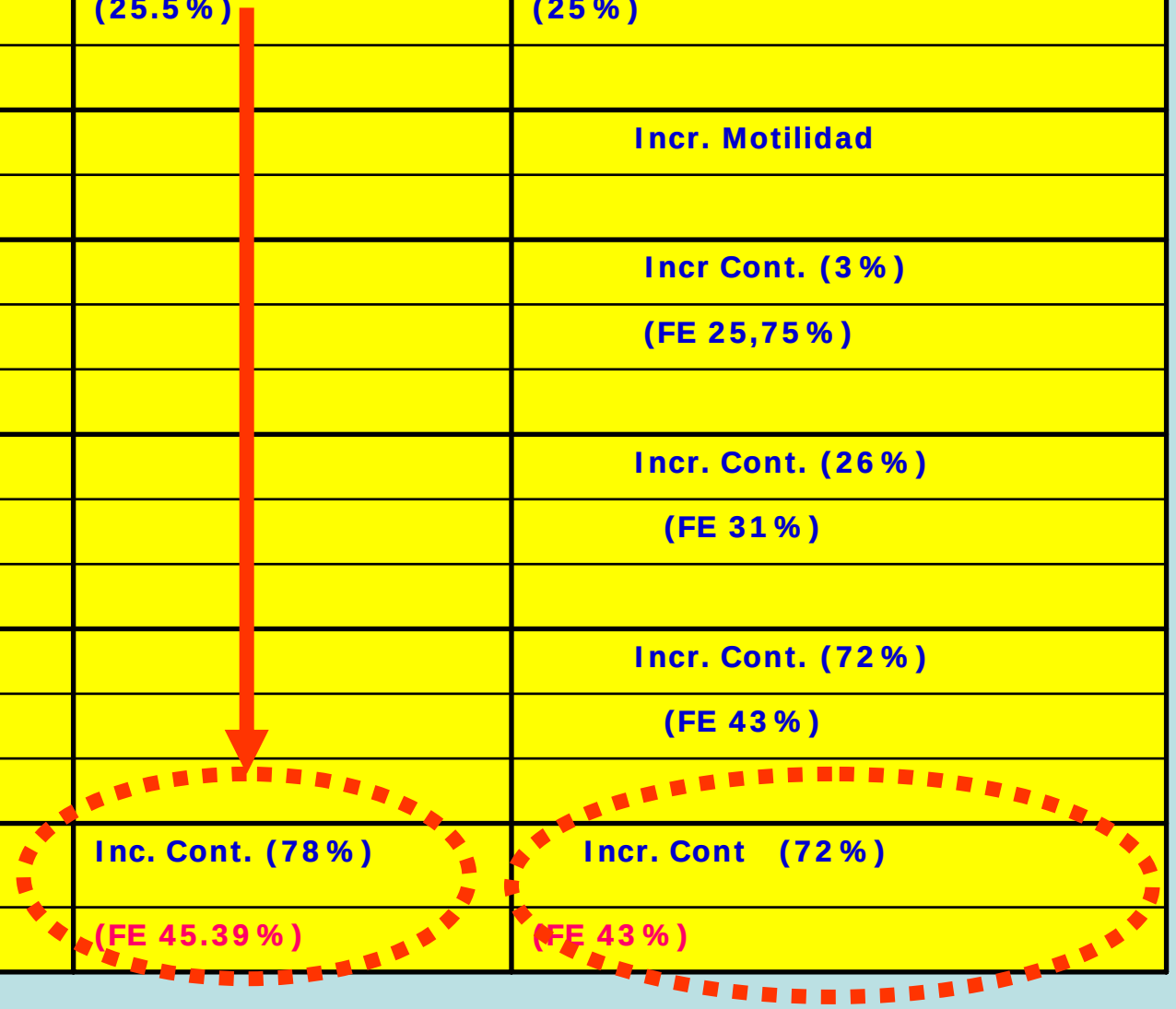
The average of Mononuclears Cells obtained was 569 x 10 p6, the average of cells with CD 34 (+)marked was 22,5 x 10p6 and the average of mononuclears cells with CD34(+) & CD38(-) was 3,07 x 10p6.





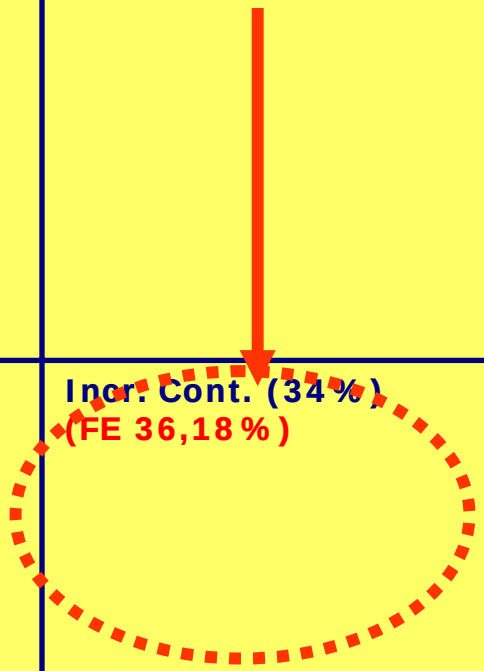
Fundación Don Roberto Fernandez Viña

Group Stems cells	FEY VI	FE EC0
Día 0	(25.5%)	(25%)
Día 7		Incr. Motilidad
Día 14		Incr Cont. (3%)
		(FE 25,75%)
Día 25/45		Incr. Cont. (26%)
		(FE 31%)
Día 60		Incr. Cont. (72%)
		(FE 43%)
Día 90/100	Inc. Cont. (78%)	Incr. Cont (72%)
	(FE 45.39%)	(FE 43%)



Control Group Follow up

Control Group	FE VI	FE Ecoc.
Día 0	(27%)	(25.5%)
Día 90		Incr. Cont. (30%) (FE 33.15%)
Día 90/100	Incr. Cont. (34%) (FE 36,18%)	Incr. Cont. (30%) (FE 33.15%)



Follow up (3 month)
Comparison both groups

Control Group	Cells therapy Group
FE basal Vi average : 27%	FE basal Vi average:25.5%
FE Ecoc. Basal (25.5%)	FE Ecoc. Basal (25%)
FE Eco 30/60 dias(12% improve	FE Eco30/60 dias(26% improve)
FE Eco 90 dias (30% improve)	FE Eco 90 dias (improve72%)
FE Vi 90 dias (34% improve)	FE Vi 90 dias.(improve78%)
Reestenosis In stent.... 12%	Reestenosis in Stent 0%

Fundación
Don Roberto
Fernandez Viña

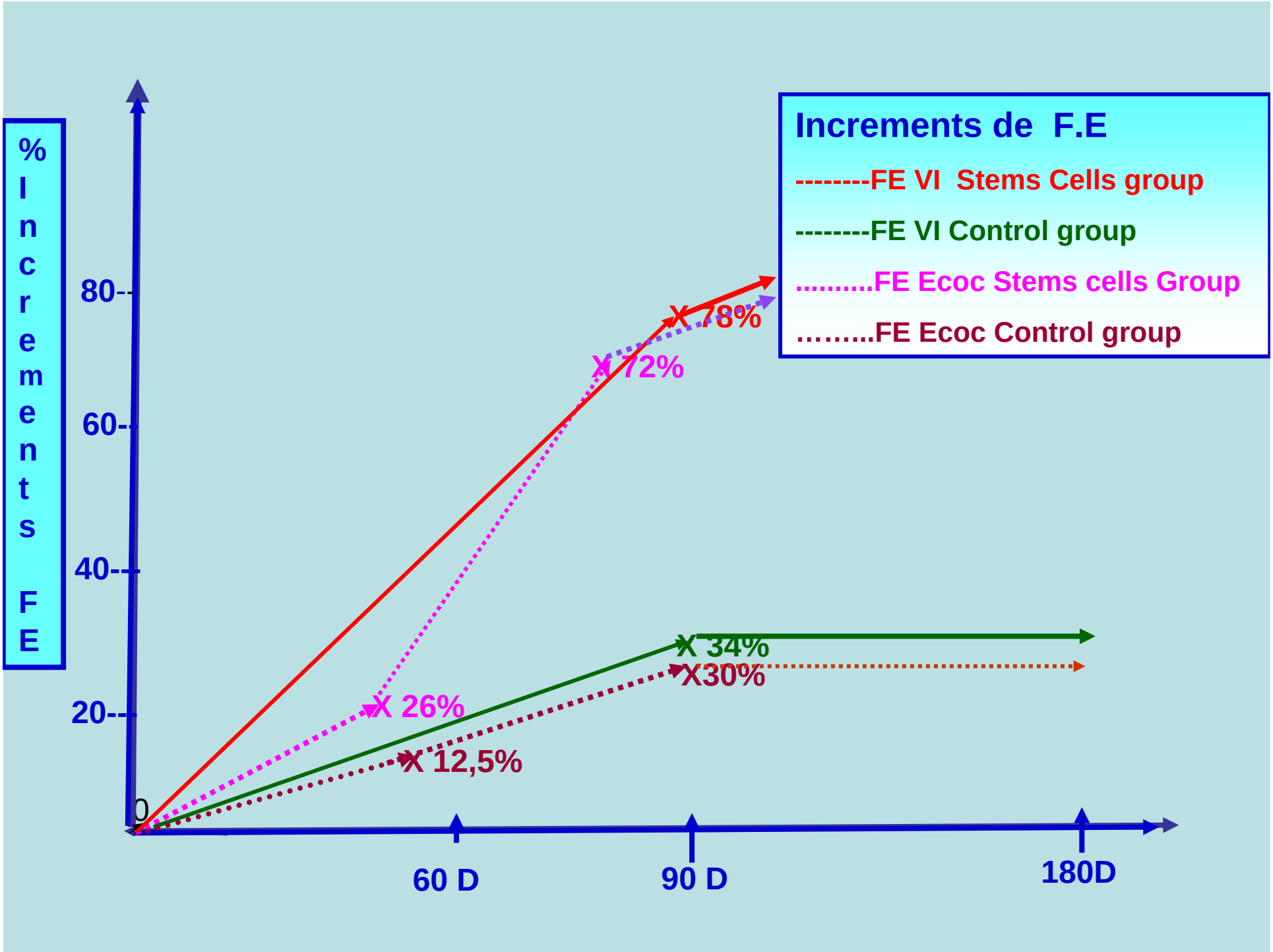
Control Group

Grupo control	FE VI	FE Ecoc.
Día 0	(27%)	(25.5%)
Día 90		Incr. Cont. (30%) (FE 32.10%)
Día 90 /	Incr. Cont. (34%) (FE 36,18%)	Incr. Cont. (30%) (FE 33.15%)

Stems cells Implant Group

Grupo Stems cells	FEY VI	FE EC0
Día 0	(25.5%)	(25%)
Día 7		Incr. Motilidad
Día 14		Incr Cont. (3%) (FE 25,75%)
Día 25 / 45		Incr. Cont. (26%) (FE 31%)
Día 60		Incr. Cont. (72%) (FE 43%)
Día 90 /	Inc. Cont. (78%) (FE 45.39%)	Incr. Cont (72%) (FE 43%)

Fundación Don Roberto Fernandez Viña

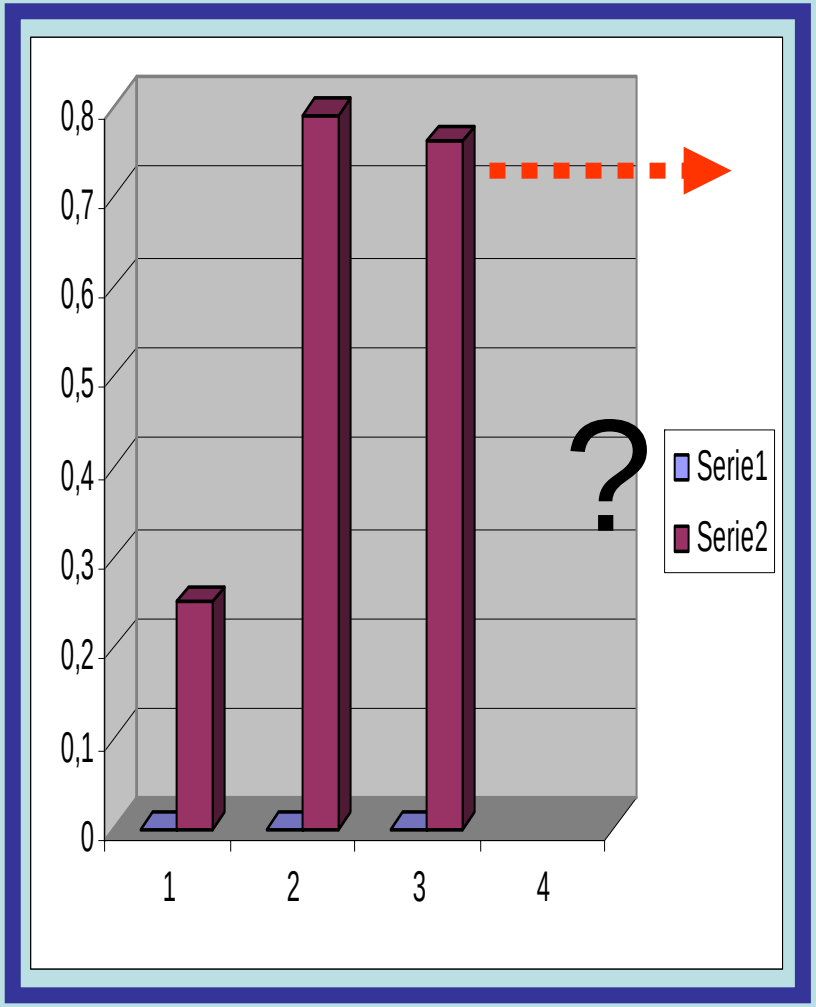

% Increments FE
80
60
40
20
0
60 D
90 D
180D
X 78%
X 72%
X 26%
X 34%
X30%
X 12,5%
Increments de F.E
--------FE VI Stems Cells group
--------FE VI Control group
.....FE Ecoc Stems cells Group
……..FE Ecoc Control group

Conclusions

The early Stems Cells implants, after a Myocardial Infarction in which the culprit vessel has been able to be open and with intra-arterial coronary injection with occlusion of the coronary vein to the effects of to produce stagnation of the coronary flow to with bigger quantity of cells has demonstrated excellent results in the recovery of the ventricles that has suffered a great Myocardial Infarction in 3 months of these patients' follow up.

But the Millions Question was

- ¿IS THE IMPROVEMENT IN E.F CREATED BY STEMS CELLS IMPLANTATION POST-MI MAINTAINED AFTER LONG TERM FOLLOW UP?

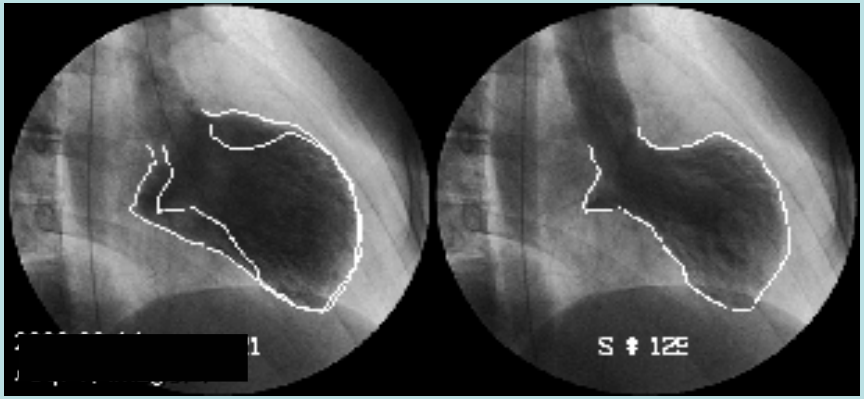


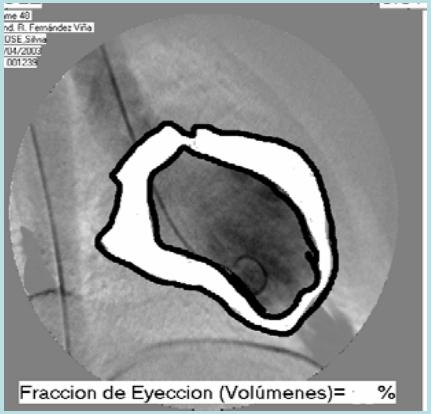
Follow up after long time
STEM CELL IMPLANTED GROUP

- **After 180 days** we performed a new coronariography and ventriculography.
- All the Stents were permeable.
- EF performed was maintanied in 76% in relationship with basal EF.
- No deterioration of the contractile function was observed
- In any of the patients did we observe any M.A.C.E.
- One patient died of unrelated causes in the cell group

PRE IMPLANT

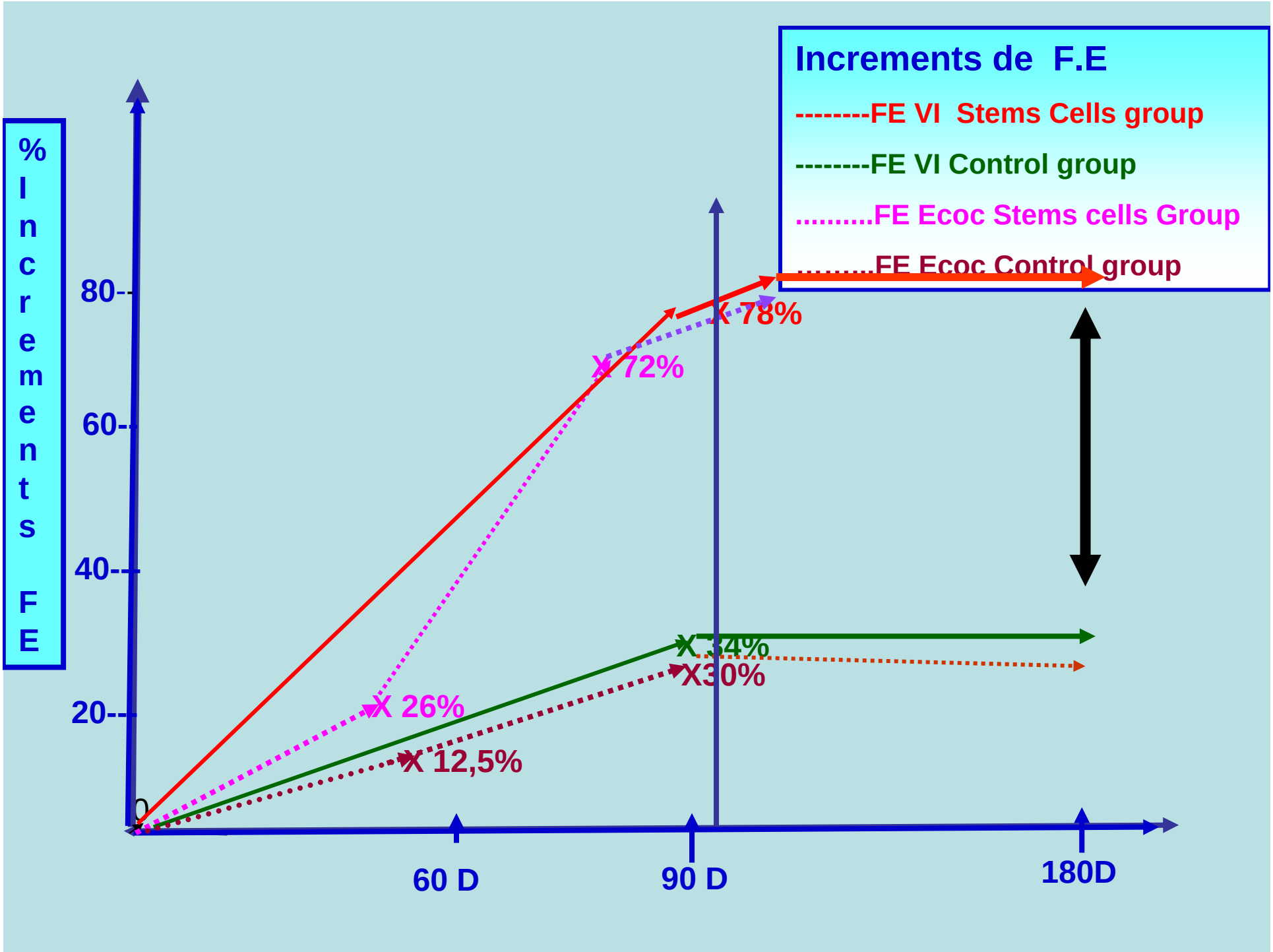
POST IMPLANT 180 days





Follow up after long time CONTROL GROUP

- **After 180 days we performed a coronariography and ventriculography**
- **23% reestenosis in Stent in the control group**
- **EF performed was maintanied 35 % in relationship with basal EF.**
- **MACE were verified in 15% of the patients**

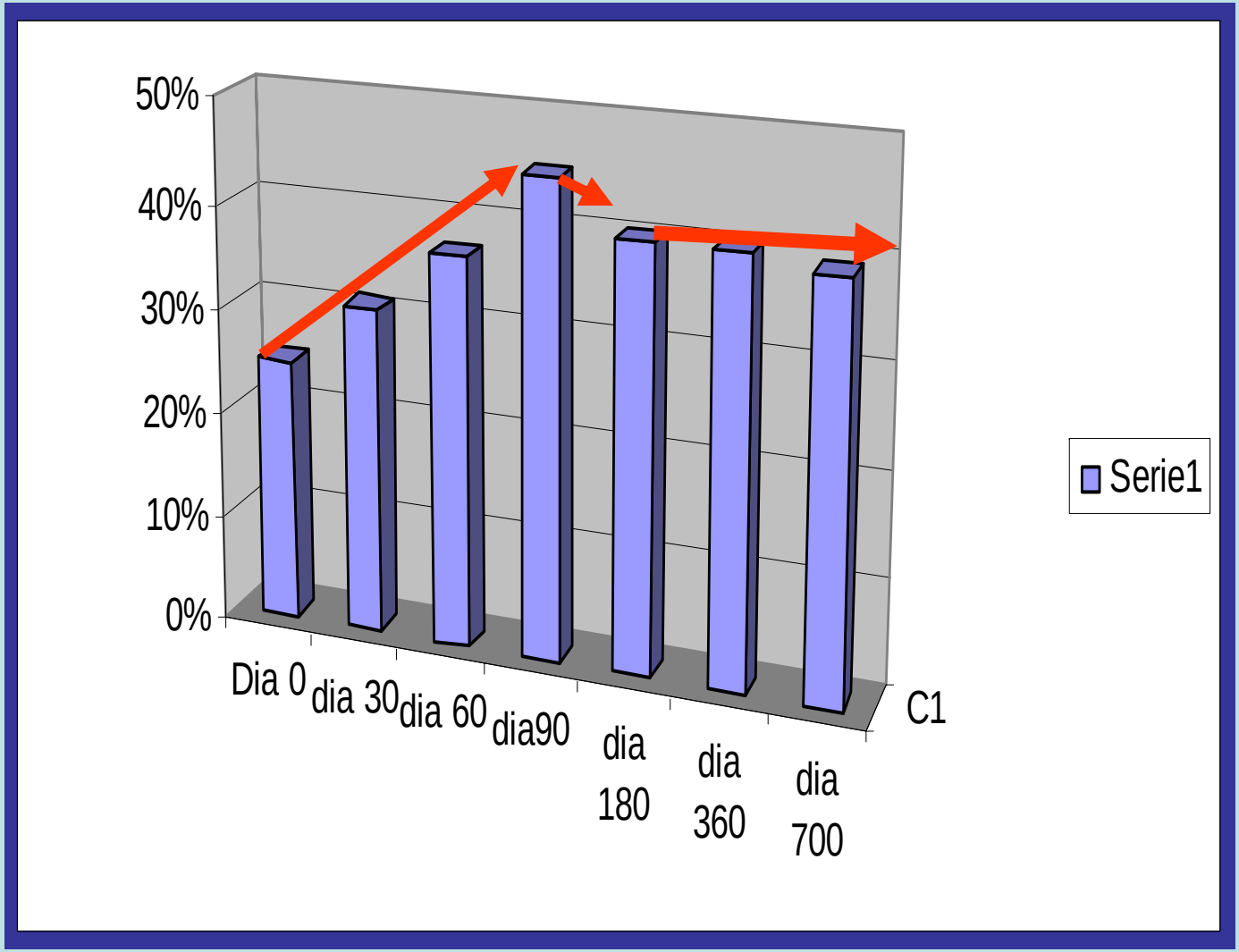

Increments de F.E
--------FE VI Stems Cells group
--------FE VI Control group
.....FE Ecoc Stems cells Group
.....FE Ecoc Control group
% Increments FE
80
60
40
20
0
X 78%
X 72%
X 26%
X 34%
X30%
X 12,5%
60 D
90 D
180D

Follow up (2 YEARS)

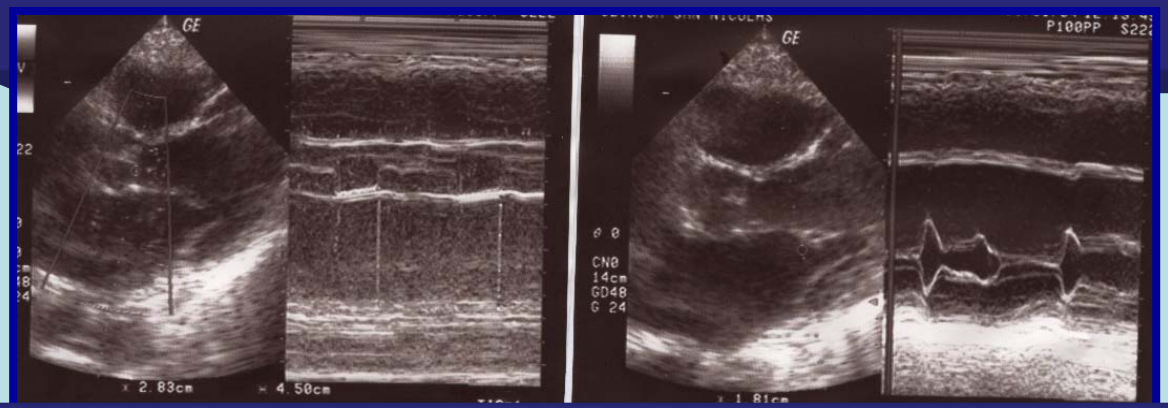
Follow up After 720 Days

STEM CELLS IMPLANTED GROUP

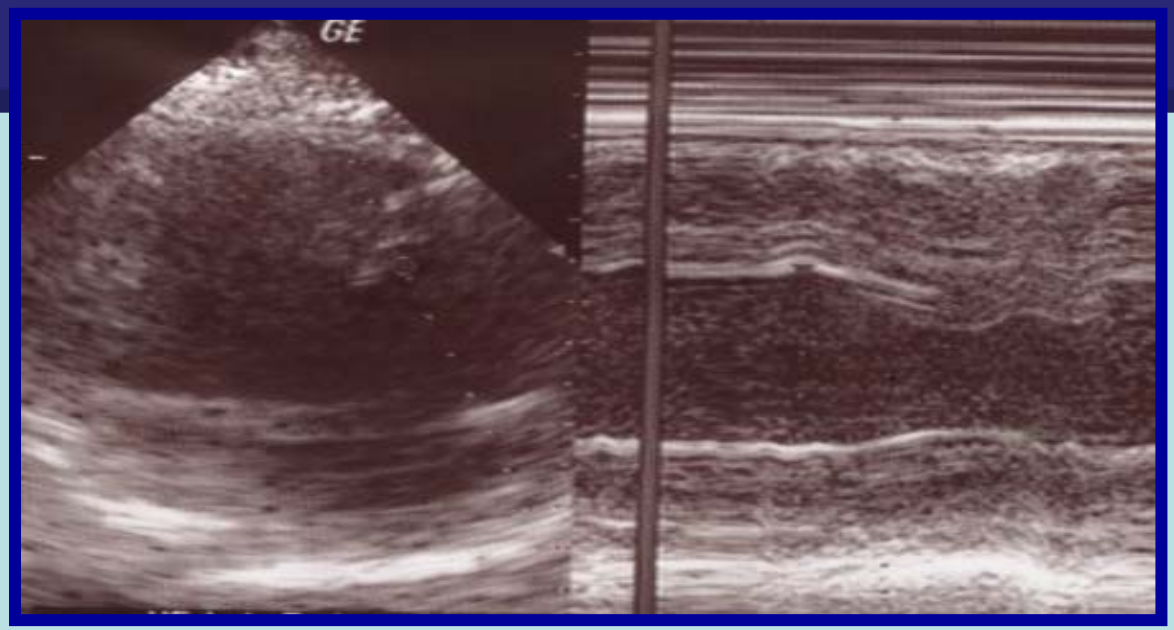
- **No deterioration of the contractile function was observed in any of the patients**
- **In during the follow up period, nor did we observe any MACE.**
- **It was not observed any dead patients in relationship with coronariopathy**


50%
40%
30%
20%
10%
0%
Dia 0
dia 30
dia 60
dia90
dia 180
dia 360
dia 700
C1
Serie1

Echocardiogram pre implant



Echocardiogram postimplant after 2 years (same patient)



Fundación
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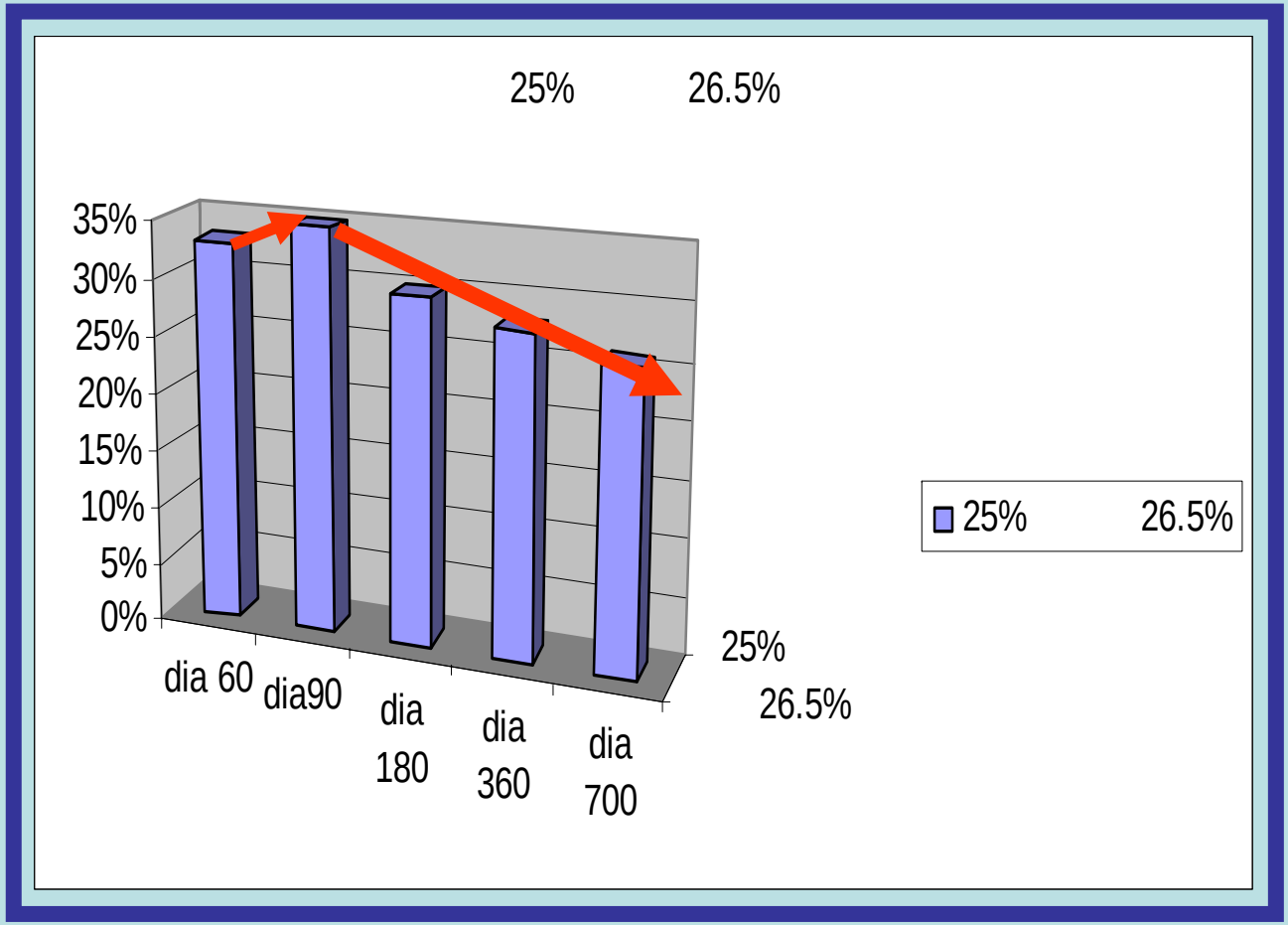
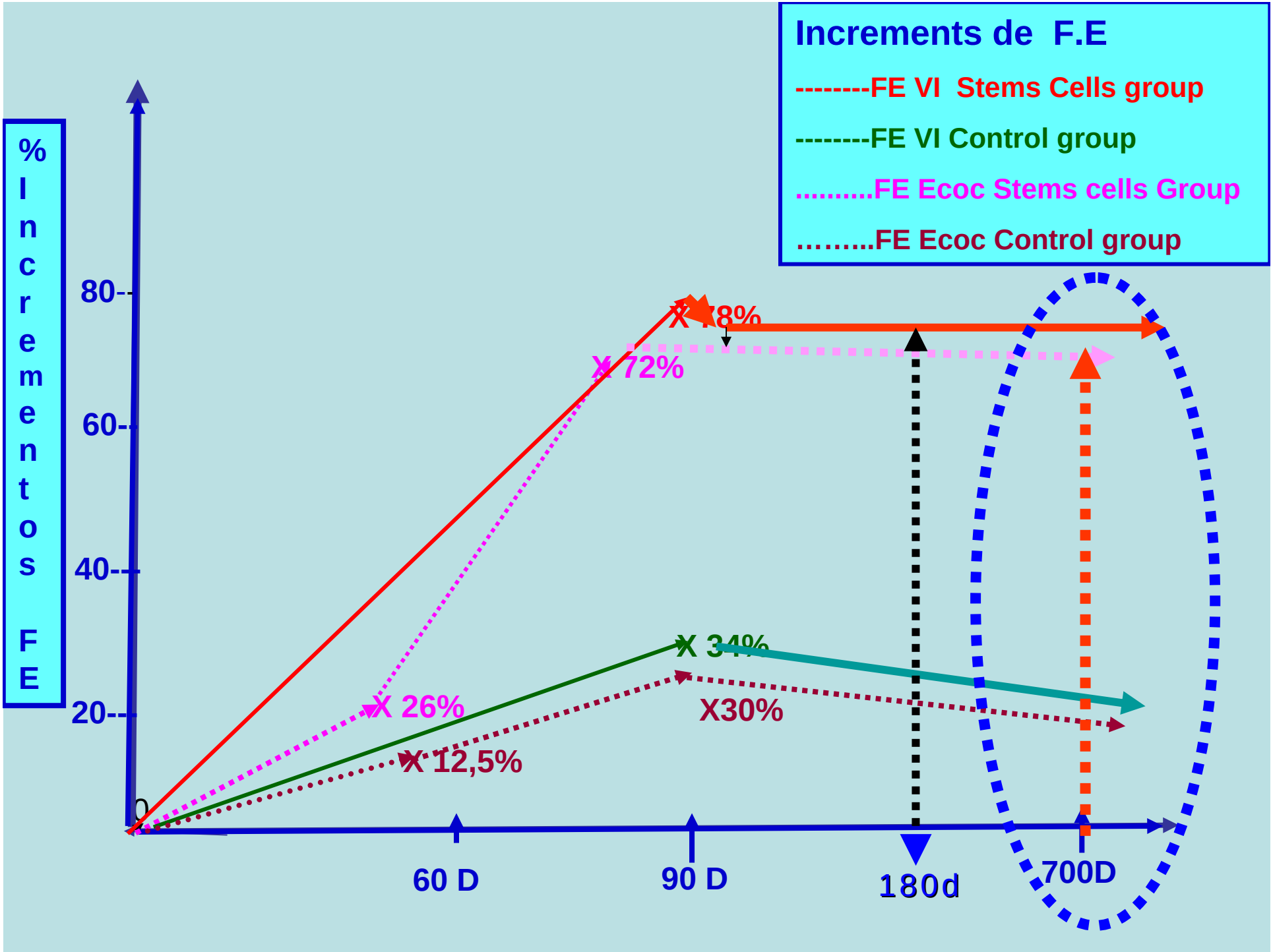
Fernandez Viña

Follow up After 720 Days

CONTROL GROUP

- Deterioration of the contractile function was observed in the majority of the patients (90%)
- In during the follow up period, MACE were verified in 35% of the patients
- EF had decreased by 16% with respect to EF measured at 180 days.
- 3 patients dead was observed in the control group (1.10%),
-

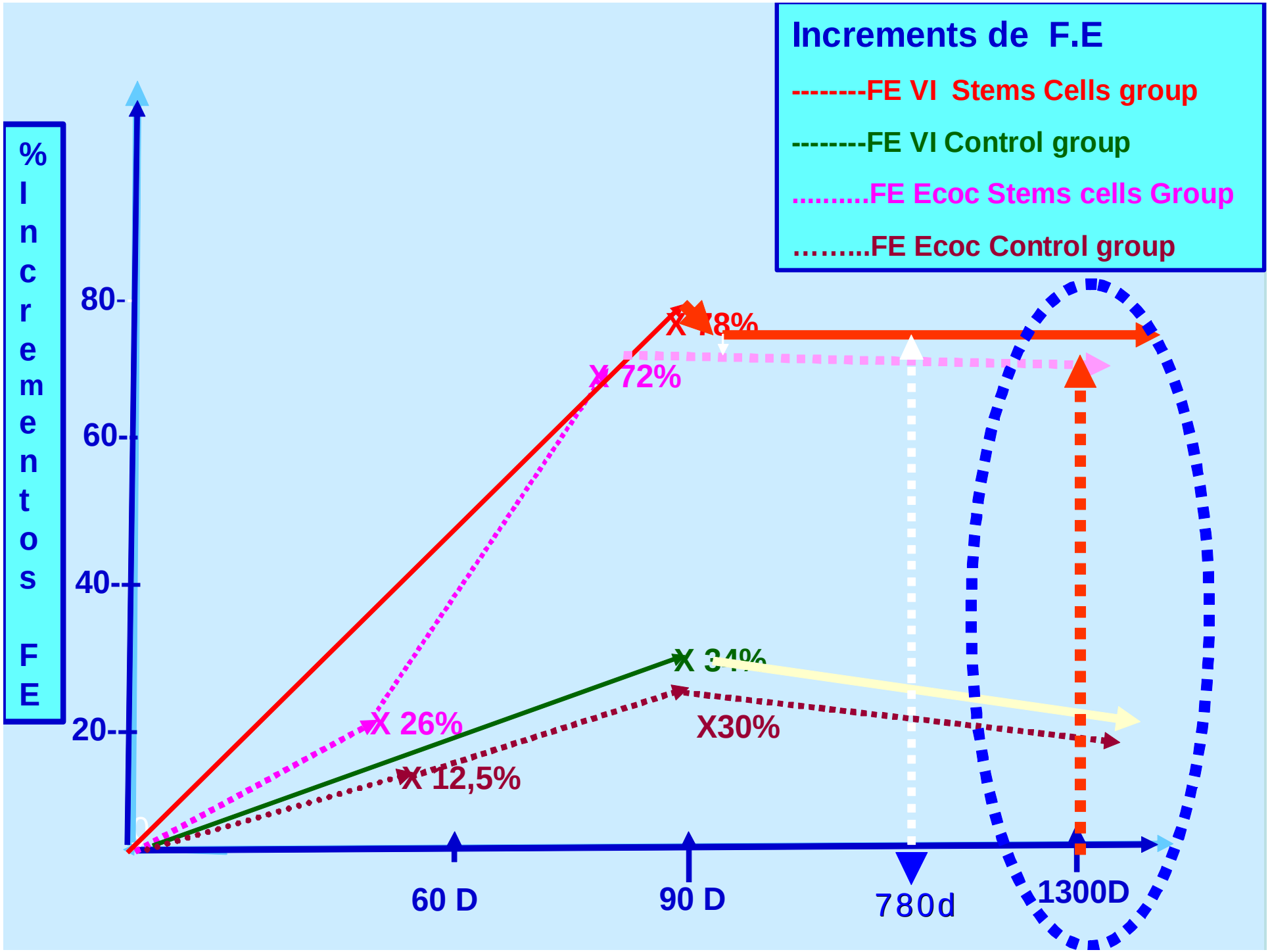

25%
26.5%
35%
30%
25%
20%
15%
10%
5%
0%
dia 60
dia90
dia 180
dia 360
dia 700
25%
26.5%
25%
26.5%


Increments de F.E
--------FE VI Stems Cells group
--------FE VI Control group
.....FE Ecoc Stems cells Group
.....FE Ecoc Control group
% Incrementos FE
80
60
40
20
0
X 78%
X 72%
X 26%
X 34%
X30%
X 12,5%
60 D
90 D
180d
700D

Follow up five years

- After five years (5)
- Stem Cell group : The EF gained decreased 1,5%

  meantime
- Control Group lost 21% of EF with respect to EF measured at first year.


Increments de F.E
--------FE VI Stems Cells group
--------FE VI Control group
.....FE Ecoc Stems cells Group
……..FE Ecoc Control group
% Incrementos FE
80
60
40
20
X 72%
X 26%
X 12,5%
X30%
60 D
90 D
780d
1300D

..... so the answer for the Millions Question

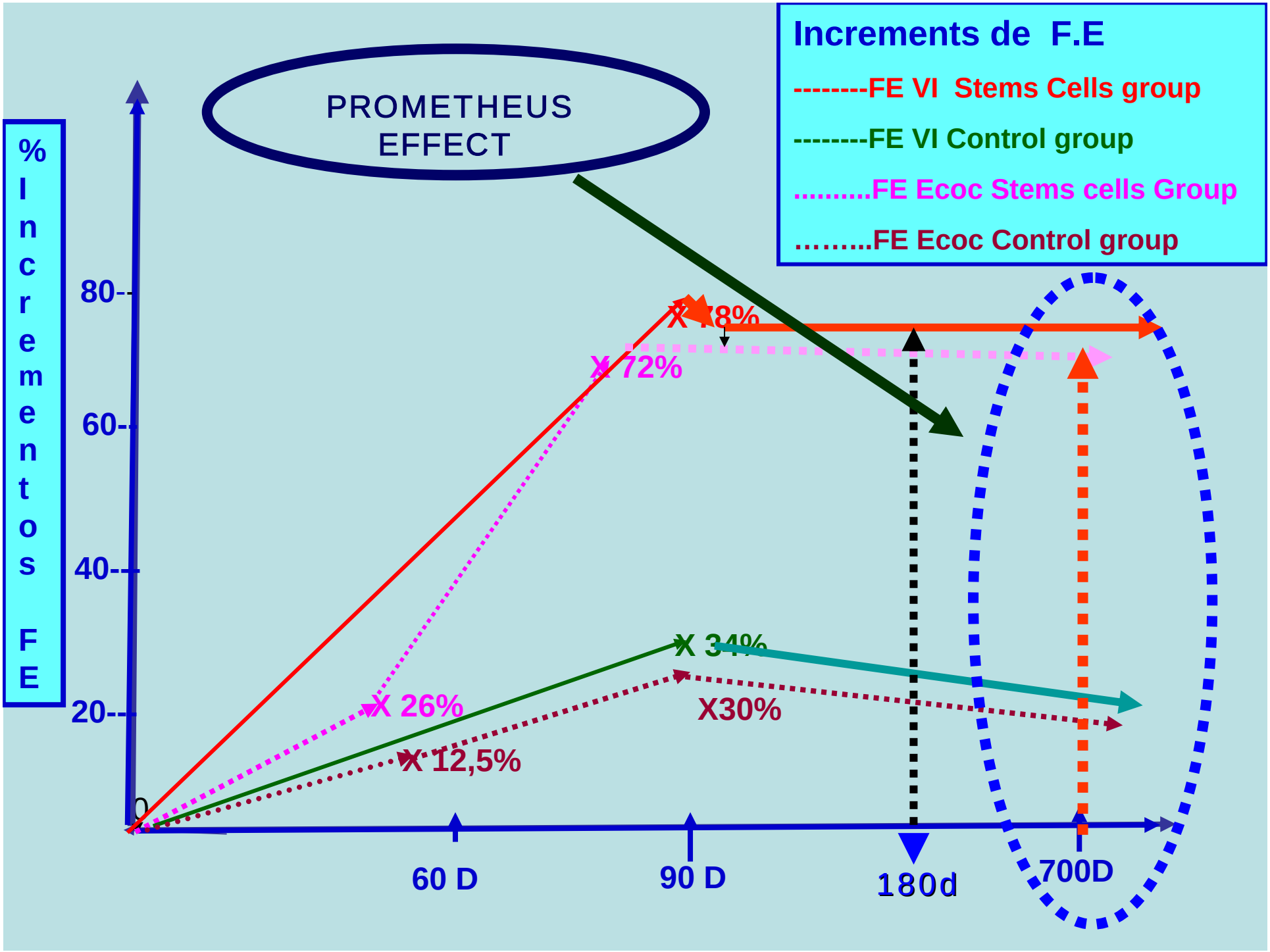
¿IS THE IMPROVEMENT IN EJECTION FRACTION CREATED BY STEMS CELLS IMPLANTATION POST-MYOCARDIAL INFARCTION MAINTAINED AFTER LONG TERM FOLLOW UP?

..... yes

THE IMPROVEMENT IN EJECTION FRACTION CREATED BY STEMS CELLS IMPLANTATION POST-MYOCARDIAL INFARCTION

IS MAINTAINED AFTER LONG TERM FOLLOW UP

- The Prometheus Effect has been succeeded
- So...The Legend and the Mythology is true???
- **Have we descript a new and true effects of Stems Cells in Heart repair ????**


PROMETHEUS EFFECT
Increments de F.E
--------FE VI Stems Cells group
--------FE VI Control group
.....FE Ecoc Stems cells Group
.....FE Ecoc Control group
% Incrementos FE
80
60
40
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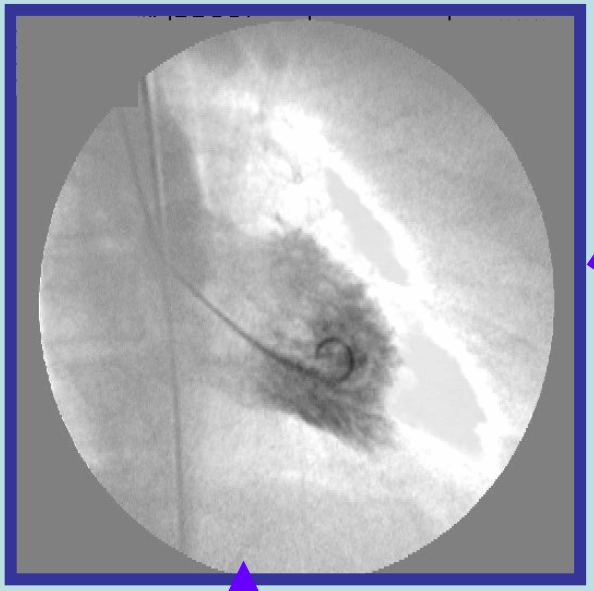
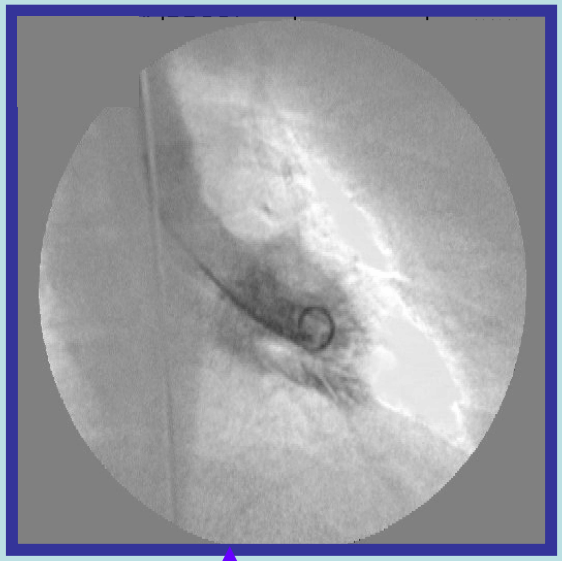
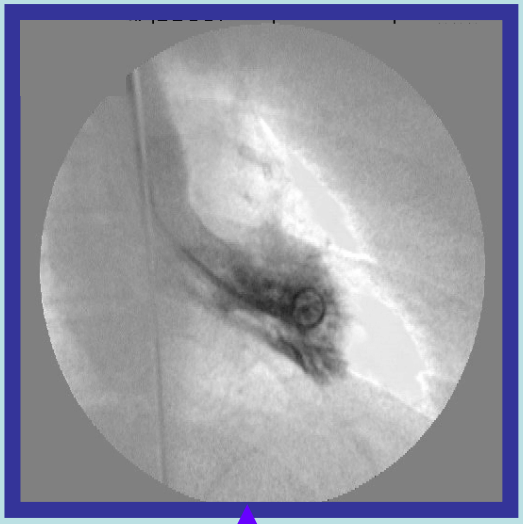
0
X 78%
X 72%
X 26%
X 34%
X30%
X 12,5%
60 D
90 D
180d
700D



I.A.M



90 Days POST IMPLANT



5 Years POST IMPLANT

BUILDING ENDOVASCULAR SYNERGIES

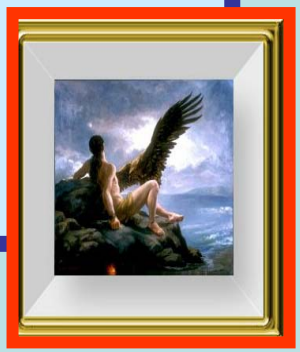
MEET 2008

MULTIDISCIPLINARY EUROPEAN ENDOVASCULAR THERAPY

www.meetcongress.com

Conclusions :

The implant of Mononuclear bone marrow Cells (Stems Cells) after an AMI improves the performance of the left ventricle which is maintained in the time (5 years) and it seems to diminish Coronary Stent reestenosis at least in immediate form.



Miocardyal Infarction Repair with intracoronary implant of Autologous Stem cells

Improvement of Ventricular Functión & Isquemia

Estudio TECELCOR (TErapia CELular CORazón) Argentina

Authors: Roberto Fernández Viña MD , et al.

FUNDACION MAPFRE MEDICINA

INSTITUTO MAPFRE DE MEDICINA CARDIOVASCULAR

Diploma

POR EL

PREMIO A LAS MEJORES COMUNICACIONES IBEROAMERICANAS 2004

que ha sido otorgado a los Dres.
Roberto Fernández Viña, Oberdan Andrin, Francisco Vrsalovick, Federico Benetti, Marcelo Fernández Viña, Andrés Pinto y Jorge Saslavsky,
del Centro Cardiovascular Fundación Don Roberto Fernández Viña, Fundación Benetti y Clínica San Nicolás, de Buenos Aires, Argentina.

por el trabajo titulado:
"Reparación de Infarto de Miocardio con Implante Coronario de Stems cells (Tecelcor)"
presentado en el Congreso de las Enfermedades Cardiovasculares (Congreso Nacional de la Sociedad Española de Cardiología), celebrado en Madrid, del 20 al 23 de octubre de 2004.

Madrid, 20 de octubre de 2004

Dr. Jesús M. Paylos González
Director
Instituto MAPFRE de Medicina Cardiovascular

D. Carlos Alvarez Jiménez
Presidente
Fundación MAPFRE MEDICINA

La Sociedad Española de Cardiología

Comprometida en la salud cardiovascular

HA CONCEDIDO EL

PREMIO FUNDACIÓN MAPFRE MEDICINA A LAS MEJORES COMUNICACIONES IBEROAMERICANAS DEL CONGRESO DE LAS ENFERMEDADES CARDIOVASCULARES 2004

Al trabajo:

"REPARACIÓN DE INFARTO DE MIOCARDIO CON IMPLANTE INTRACORONARIO DE STEMS CELLS (TECELCOR)"

De los Autores:

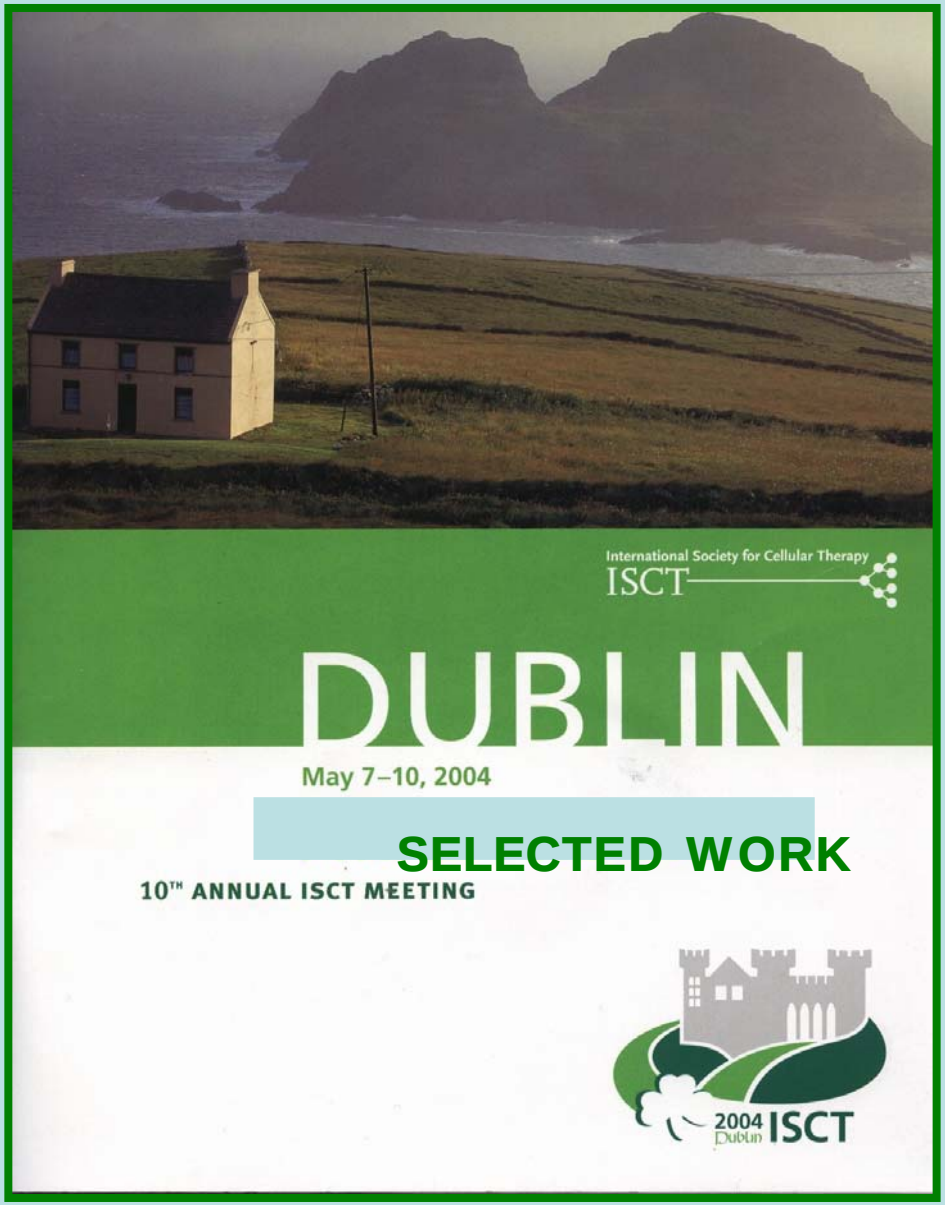
ROBERTO FERNÁNDEZ VIÑA, OBERDAN ANDRIN, FRANCISCO VRSALOVICK, FEDERICO BENETTI, MARCELO FERNÁNDEZ VIÑA, ANDRÉS PINTO Y JORGE SASLAVSKY

Por la Sociedad Española de Cardiología:
El Presidente,

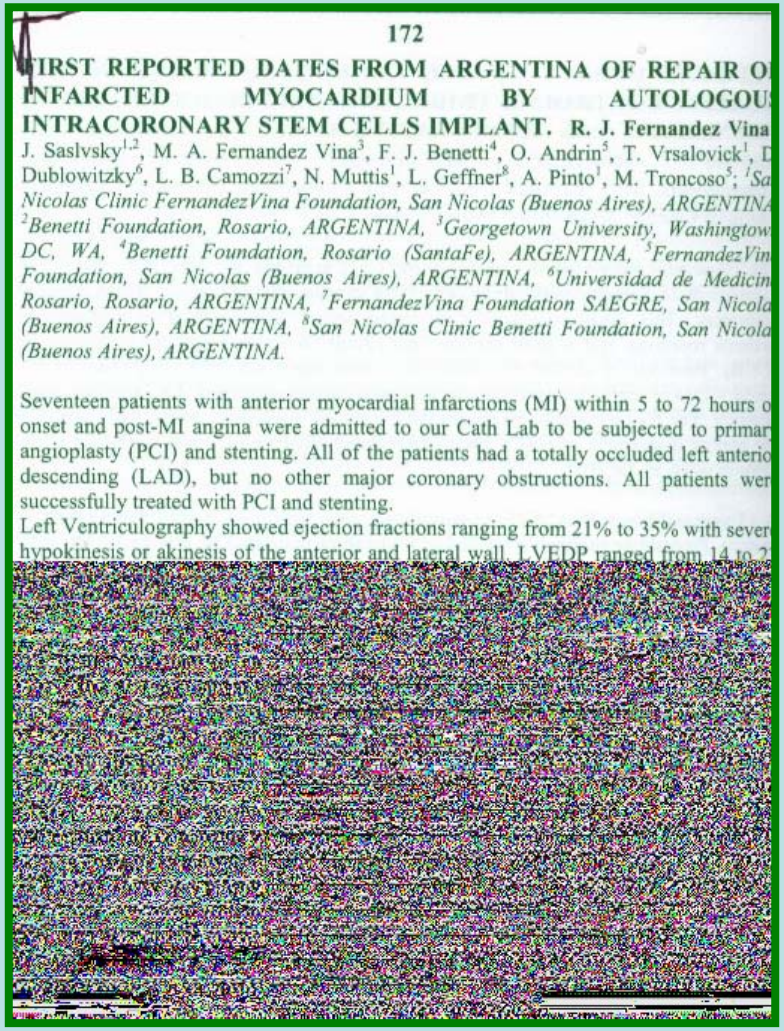
El Secretario,

Por la Fundación MAPFRE MEDICINA,

Madrid, 20 de Octubre de 2004



SELECTED WORK



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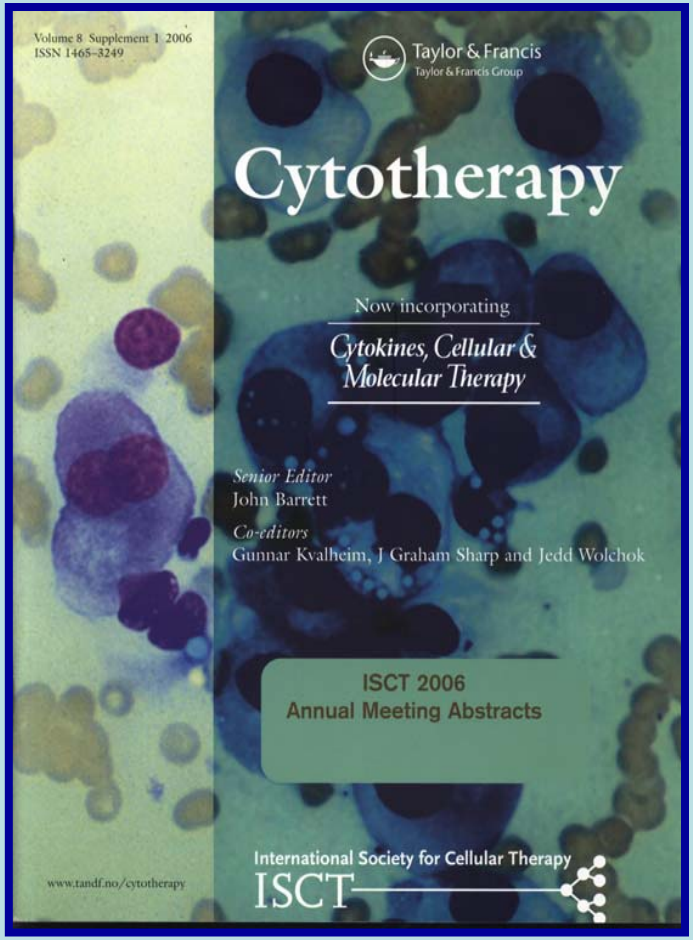
FIRST REPORTED DATES FROM ARGENTINA OF REPAIR O INFARCTED MYOCARDIUM BY AUTOLOGOU INTRACORONARY STEM CELLS IMPLANT. **R. J. Fernandez Vina**

J. Saslvsky[1,2], M. A. Fernandez Vina[3], F. J. Benetti[4], O. Andrin[5], T. Vrsalovick[1], D Dublowitzky[6], L. B. Camozzi[7], N. Muttis[1], L. Geffner[8], A. Pinto[1], M. Troncoso[5]; *[1]San Nicolas Clinic FernandezVina Foundation, San Nicolas (Buenos Aires), ARGENTINA, [2]Benetti Foundation, Rosario, ARGENTINA, [3]Georgetown University, Washington DC, WA, [4]Benetti Foundation, Rosario (SantaFe), ARGENTINA, [5]FernandezVina Foundation, San Nicolas (Buenos Aires), ARGENTINA, [6]Universidad de Medicin Rosario, Rosario, ARGENTINA, [7]FernandezVina Foundation SAEGRE, San Nicola (Buenos Aires), ARGENTINA, [8]San Nicolas Clinic Benetti Foundation, San Nicola (Buenos Aires), ARGENTINA.*

Seventeen patients with anterior myocardial infarctions (MI) within 5 to 72 hours o onset and post-MI angina were admitted to our Cath Lab to be subjected to primar angioplasty (PCI) and stenting. All of the patients had a totally occluded left anterio descending (LAD), but no other major coronary obstructions. All patients wer successfully treated with PCI and stenting.

Left Ventriculography showed ejection fractions ranging from 21% to 35% with sever hypokinesis or akinesis of the anterior and lateral wall. LVEDP ranged from 14 to 2

- ***The 12th Annual Meeting of the International Society for Cellular Therapy***
- **May 4 – 7, 2005 Berlin, Germany**
- **Maritim proArte Hotel**
- **Friedrichstra 151.**



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IS THE IMPROVEMENT IN EJECTION FRACTION CREATED BY STEMS CELLS IMPLANTATION POST MYOCARDIAL INFARCTION MAINTAINED AFTER LONG TIME FOLLOW UP?

R. J. Fernandez Vina[1], J. Saslavsky[2], R. Fernandez Viña[3], O. Andrin[1], F. Vrsalovick[4], N. Muttis[1], S. Murad Neto[5], D. Dudoblisnky[6], J. Tuma[7], R. De Mouras[8], P. Andres[1], L. Camozzi[9], C. D Adamo[10], F. Benetti[11], M. Fernandez Viña[12]; *[1]San Nicolas Clinic FernandezVina Foundation, San Nicolas (Buenos Aires), ARGENTINA, [2]Universidad Nacional de Rosario, Rosario, ARGENTINA, [3]Universidad Maimonides Buenos Aires, Buenos Aires), ARGENTINA, [4]San Nicolas Clinic Interventional Cardiology, San Nicolas (Buenos Aires), ARGENTINA, [5]Instituto de pos Graduacion de Univ. Rio de Janeiro, Rio de Janeiro, BRAZIL, [6]Universidad Medicina Rosario Argentina, Rosario, ARGENTINA, [7]Clinica San Felipe Peru, Lima, PERU, [8]Instituto de pos Graduacion de Univ. Rio de Janeiro, Rosario, BRAZIL, [9]Fernandez Viña Foundation SAEGRE, San Nicolas (Buenos Aires), ARGENTINA, [10]San Nicolas Clinic Chief Internal Medicne, San Nicolas (Buenos Aires), ARGENTINA, [11]San Nicolas Clinic Benetti Foundation, Buenos Aires), ARGENTINA, [12]MD Anderson Medical Center, Houston, TX.*

Objectives: To evaluate the long time performance of the Left Ventricular function of Acute Myocardial Infarction treated with Stems cells implant. **Method**: 32 patients that suffered AMI were treated with primary PTCA with Stents. The Ventriculography Ejection Fraction (EF) oscillated between 21 and 32%. Between 7 and 12 days after AMI cells were implanted via the coronary artery while occluding the Coronary Sinus. We used autologuous mononucleares cells CD 34(+) and CD38 (-), mean number of cells $22x10^6$. This group was compared with a Control Group of 26 patients that suffered an MI of similar characteristics, these patients only received PTCA and a Stent. **Results:** After 180 days we performed a coronariography and a ventriculography. In the cell group all the Stents were permeable, versus 23% reestenosis in the control group. In the cell group EF improved by an average of 76% in relationship to the basal EF versus 35% in the control group.. The patients were followed up for up to 2 years. During this period EF was verified using serial echocardiograms. No deterioration of the contractile function was observed in any of the patients in the cell group during the follow up period, nor did we observe any MACE. In the control group MACE were verified in 35% of the patients. One patient died of unrelated causes in the cell group vs. 3 in the control group (1.10%), in these patients EF had decreased by 16% with respect to EF measured at 180 days. **Conclusions**: The implant of Mononuclear bone marrow Cells (Stems Cells) after an AMI improves the performance of the left ventricle which is maintained in the time (2 years) and it seems to diminish Coronary Stent reestenosis at least in immediate form.

ISCT BERLIN 2006

Oral Abstract Presentations: Best Abstract Session
Saal B/C

18:00-18:10	INFUSION REACTIONS ASSOCIATED WITH ADMINISTRATION OF STERILE AND NON-STERILE HEMATOPOIETIC PROGENITOR CELLS: A RETROSPECTIVE REVIEW OF 2062 TRANSPLANTS	Dennis	Gastineau	262
18:15-18:25	ABSOLUTE NUMBER OF TRANSPLANTED CD34+ CELLS EXPRESSING C-MPL (CD110) CORRELATES WITH SPEED OF PLATELET ENGRAFTMENT FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANTATION	Mary	Sartor	265
18:30-18:40	T CELL IMMUNOTHERAPY FOR ADENOVIRAL INFECTIONS OF STEM CELL TRANSPLANT RECIPIENTS	Ann	Leen	274
18:45-18:55	IS THE IMPROVEMENT IN EJECTION FRACTION CREATED BY STEMS CELLS IMPLANTATION POST MYOCARDIAL INFARCTION MAINTAINED AFTER LONG TIME FOLLOW UP?	Roberto	Fernandez Vina	278

Why the differences????
BETWEEN our results and
others results of others
DIFFERENTS GROUPS
ARROUNS THE WORLS

BMSC transplantation in STEAMI in human
¿Is it safe? ¿Does it improve function?

Author	Nº	Follow-up	Method	Favourable remodeling	>EF	>Perfusion
Strauer	10	3 months	Cath DobuEcho Thalium	Yes	No	Yes
Assmuss	19	4 months	Cath PET DobuEcho Thalium	Yes	Yes	Yes
Kang	7	6 months	Cath DobuEcho	Yes	Yes	Yes
Wollert (BMCs)	30	6 months	MRI	Yes	Yes	Yes
Avilés	20	6 months	MRI EchoDobu Cath	Yes	Yes	-

Intracoronary Injection of CD133-Positive Enriched Bone Marrow Progenitor Cells Promotes Cardiac Recovery After Recent Myocardial Infarction

Feasibility and Safety

Jozef Bartunek, MD, PhD*; Marc Vanderheyden, MD*; Bart Vandekerckhove, MD, PhD; Samer Mansour, MD; Bernard De Bruyne, MD, PhD; Pieter De Bondt, MD; Inge Van Haute, MD; Nele Lootens, RN; Guy Heyndrickx, MD, PhD; William Wijns, MD, PhD

Background—Bone marrow CD133-postive ($CD133^+$) cells possess high hematopoietic and angiogenic capacity. We tested the feasibility, safety, and functional effects of the use of enriched $CD133^+$ progenitor cells after intracoronary administration in patients with recent myocardial infarction.

Methods and Results—Among 35 patients with acute myocardial infarction treated with stenting, 19 underwent intracoronary administration of $CD133^+$ progenitor cells ($12.6\pm2.2\times10^6$ cells) 11.6 ± 1.4 days later (group 1) and 16 did not (group 2). At 4 months, left ventricular ejection fraction increased significantly in group 1 (from $45.0\pm2.6\%$ to $52.1\pm3.5\%$, $P<0.05$), but only tended to increase in case-matched group 2 patients (from $44.3\pm3.1\%$ to $48.6\pm3.6\%$, P=NS). Likewise, left ventricular regional chordae shortening increased in group 1 (from $11.5\pm1.0\%$ to $16.1\pm1.3\%$, $P<0.05$) but remained unchanged in group 2 patients (from $11.1\pm1.1\%$ to $12.7\pm1.3\%$, P=NS). This was paralleled by reduction in the perfusion defect in group 1 (from $28.0\pm4.1\%$ to $22.5\pm4.1\%$, $P<0.05$) and no change in group 2 (from $25.0\pm3.0\%$ to $22.6\pm4.1\%$, P=NS). In group 1, two patients developed in-stent reocclusion, 7 developed in-stent restenosis, and 2 developed significant de novo lesion of the infarct-related artery. In group 2, four patients showed in-stent restenosis. In group 1 patients without reocclusion, glucose uptake shown by positron emission tomography with ^{18}fluorodeoxyglucose in the infarct-related territory increased from $51.2\pm2.6\%$ to $57.5\pm3.5\%$ ($P<0.05$). No stem cell-related arrhythmias were noted, either clinically or during programmed stimulation studies at 4 months.

Conclusion—In patients with recent myocardial infarction, intracoronary administration of enriched $CD133^+$ cells is feasible but was associated with increased incidence of coronary events. Nevertheless, it seems to be associated with improved left ventricular performance paralleled with increased myocardial perfusion and viability. (***Circulation***. **2005; 112[suppl I]:I-178–I-183.)**

Table 1
Clinical studies using bone marrow cell transplantation with control group of patients

Study reference	Patients (control)	Patients (with cells)	Cell type	Delivery mode	Adjunct procedure	Follow up (months)	Result summary	Complications
Perin et al. [93]	07	14	BMMNC	EC	ST	2 and 4	Improved LVEF and reduction in LVEDV, Significant mechanical improvement in the injected segments as assessed by 2D Echo, dipyridamole SPECT perfusion scan and NOGA EMM	One death each in the control and cell injected groups
Strauer et al. [108]	10	10	BMMNC	IC	PCI	3	Significant reduction in infarct size Improved infarct wall motion, improved stroke volume index, LVEF and regional perfusion by DS Echo, radionuclide ventriculography	None
Assmus et al. [110]	09	20	BMMNC/CPC	IC	PCI	4	Improved regional wall motion in the infarct area, enhanced LVEF, profoundly reduced LVEFV, enhanced viability in the infarct zone by DS Echo, quantitative PET scan	
Chen et al. [109]	35	34	BMMNC	IC	PCI		Improved wall velocity in the infracted Segments, reduction in the perfusion defects, improved LVEF, significantly reduced LVESV by Echo, NOGA EMM, PET scanning	None
Wollert et al. [114]	30	30	CD34+	IC	PCI	06	Improved LVEF, 24 h Holter monitoring, functional MRI	

BMMNC: bone marrow mononuclear cells; **DS-Echo**: dobutamine stress echocardiography; **Echo**: echocardiography; **EMM**: electro mechanical mapping; **IC**: intracoronary; **LVESV**: left ventricular end systolic volume; **MRI**: magnetic resonance imaging; **PCI**: percutaneous coronary intervention; **PET**: positron emission tomography.

Clinical Investigation and Reports

Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI)

Birgit Assmus, MD; Volker Schächinger, MD; Claudius Teupe, MD; Martina Britten, MD; Ralf Lehmann, MD; Natascha Döbert, MD; Frank Grünwald, MD; Alexandra Aicher, MD; Carmen Urbich, PhD; Hans Martin, MD; Dieter Hoelzer, MD; Stefanie Dimmeler, PhD; Andreas M. Zeiher, MD

Background—Experimental studies suggest that transplantation of blood-derived or bone marrow–derived progenitor cells beneficially affects postinfarction remodeling. The safety and feasibility of autologous progenitor cell transplantation in patients with ischemic heart disease is unknown.

Methods and Results—We randomly allocated 20 patients with reperfused acute myocardial infarction (AMI) to receive intracoronary infusion of either bone marrow–derived (n=9) or circulating blood–derived progenitor cells (n=11) into the infarct artery 4.3±1.5 days after AMI. Transplantation of progenitor cells was associated with a significant increase in global left ventricular ejection fraction from 51.6±9.6% to 60.1±8.6% (P=0.003), improved regional wall motion in the infarct zone (−1.5±0.2 to −0.5±0.7 SD/chord; P<0.001), and profoundly reduced end-systolic left ventricular volumes (56.1±20 mL to 42.2±15.1 mL; P=0.01) at 4-month follow-up. In contrast, in a nonrandomized matched reference group, left ventricular ejection fraction only slightly increased from 51±10% to 53.5±7.9%, and end-systolic volumes remained unchanged. Echocardiography revealed a profound enhancement of regional contractile function (wall motion score index 1.4±0.2 at baseline versus 1.19±0.2 at follow-up; P<0.001). At 4 months, coronary blood flow reserve was significantly (P<0.001) increased in the infarct artery. Quantitative F-18-fluorodeoxyglucose–positron emission tomography analysis revealed a significant (P<0.01) increase in myocardial viability in the infarct zone. There were no differences for any measured parameter between blood-derived or bone marrow–derived progenitor cells. No signs of an inflammatory response or malignant arrhythmias were observed.

Conclusions—In patients with AMI, intracoronary infusion of autologous progenitor cells appears to be feasible and safe and may beneficially affect postinfarction remodeling processes. **(*Circulation*. 2002;106:3009-3017.)**

Intracoronary Bone Marrow Cell Transfer After Myocardial Infarction

Eighteen Months' Follow-Up Data From the Randomized, Controlled BOOST (BOne marrOw transfer to enhance ST-elevation infarct regeneration) Trial

Gerd P. Meyer, MD*; Kai C. Wollert, MD*; Joachim Lotz, MD; Jan Steffens, BS; Peter Lippolt, MD; Stephanie Fichtner, BS; Hartmut Hecker, MD; Arnd Schaefer, MD; Lubomir Arseniev, MD; Bernd Hertenstein, MD; Arnold Ganser; MD; Helmut Drexler, MD

Background—Intracoronary transfer of autologous bone marrow cells (BMCs) may enhance recovery of left ventricular (LV) function in patients after acute myocardial infarction (AMI). However, clinical studies addressing the effects of BMCs after AMI have covered only limited time frames ranging from 3 to 6 months. The critical question of whether BMC transfer can have a sustained impact on LV function remains unanswered.

Methods and Results–After percutaneous coronary intervention with stent implantation (PCI) of the infarct-related artery, 60 patients were randomized 1:1 to a control group with optimal postinfarction therapy and a BMC transfer group that also received an intracoronary BMC infusion 4.8±1.3 days after PCI. Cardiac MRI was performed 3.5±1.5 days, 6±1 months, and 18±6 months after PCI. BMC transfer was not associated with adverse clinical events. In the control group, mean global LV ejection fraction increased by 0.7 and 3.1 percentage points after 6 and 18 months, respectively. LV ejection fraction in the BMC transfer group increased by 6.7 and 5.9 percentage points. The difference in LVEF improvement between groups was significant after 6 months but not after 18 months (P=0.27). The speed of LV ejection fraction recovery over the course of 18 months was significantly higher in the BMC transfer group (P=0.001).

Conclusions–In this study, a single dose of intracoronary BMCs did not provide long-term benefit on LV systolic function after AMI compared with a randomized control group; however, the study suggests an acceleration of LV ejection fraction recovery after AMI by BMC therapy. **(*Circulation*. 2006;113:1287-1294.)**

Key Words: myocardial infarction ■ magnetic resonance imaging ■ cells

The TECAM project

(TErapia Celular Aplicada al Miocardio)

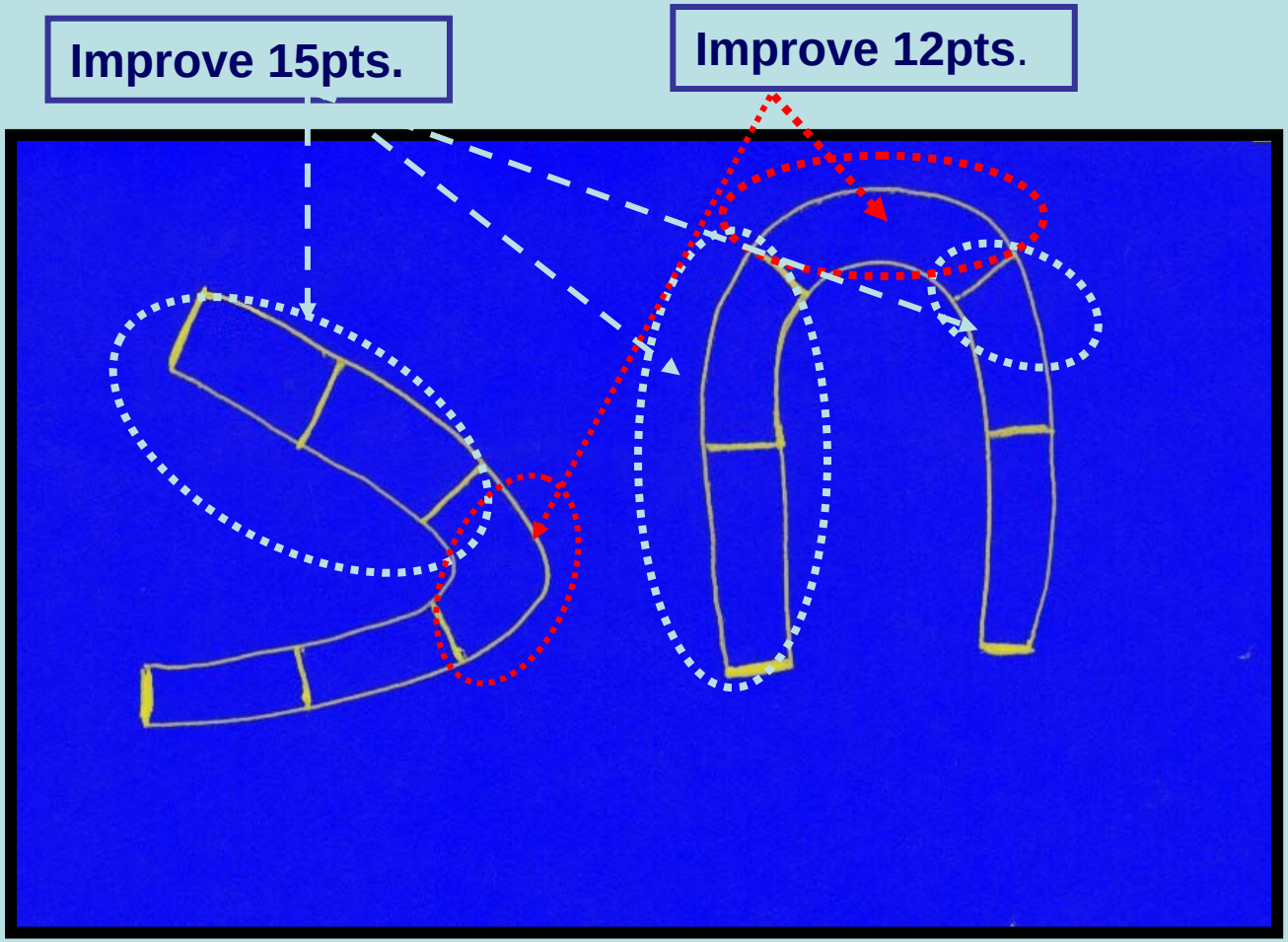
Intracoronary bone marrow cell transplantation after ST elevated myocardial infarction

Francisco F. Avilés
Instituto de Ciencias del Corazón (ICICOR)
University Hospital, Valladolid (Spain)

Cell Retention

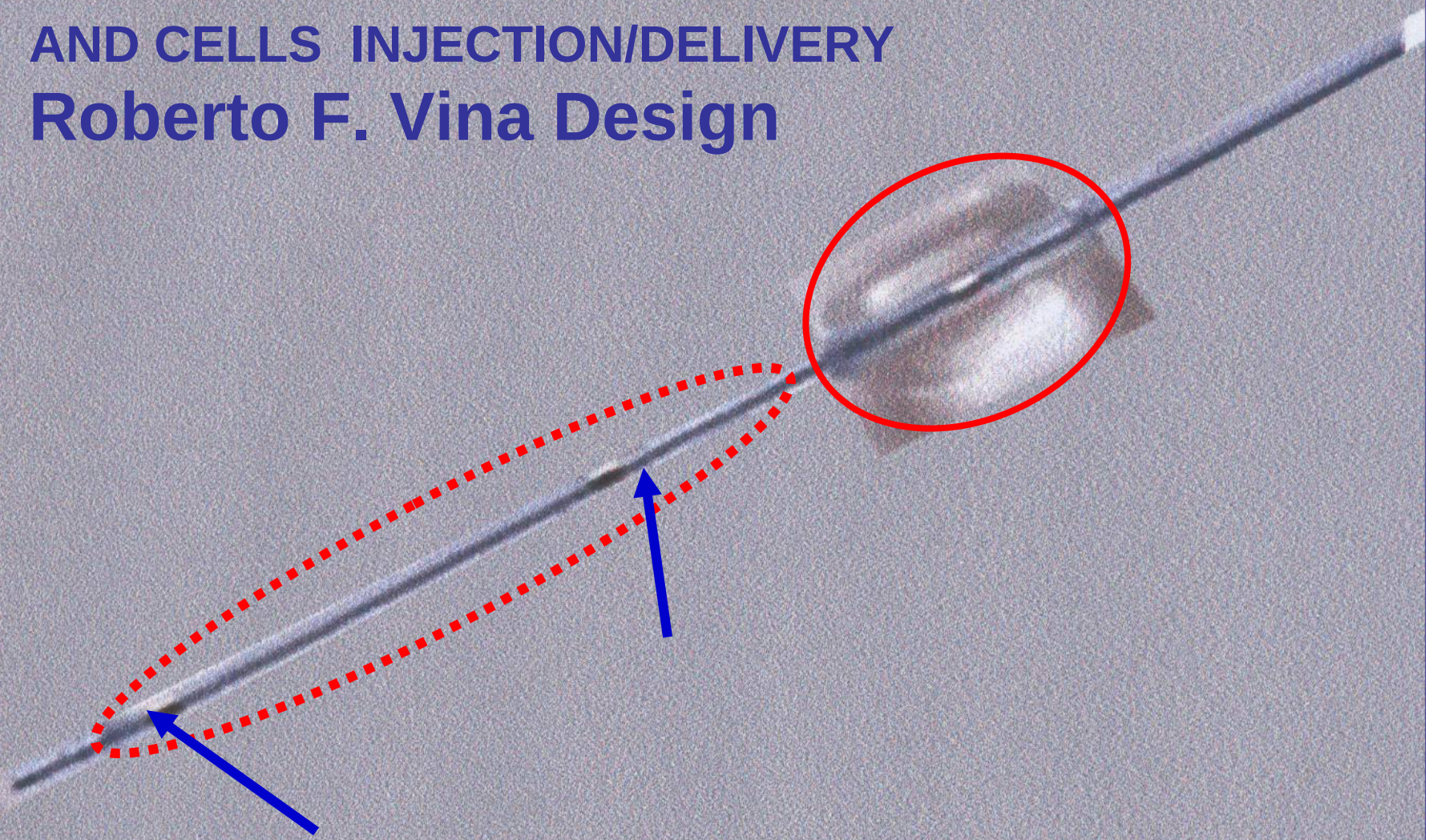
Delivery	%
Anterograde Catheter	**5**
Retrograde Catheter	**5**
Retrograde Catheter - Injection	**15**
Endocardial Catheter - Injection	**20%**
Epicardial Injection - Beating Heart	**30%**
Epicardial Injection - Arrested Heart	**40-50%**

Stems Cells Implant group: Improve of Segmentary contractility



NAOMI CATHETHER FOR DRUG-GENES AND CELLS INJECTION/DELIVERY

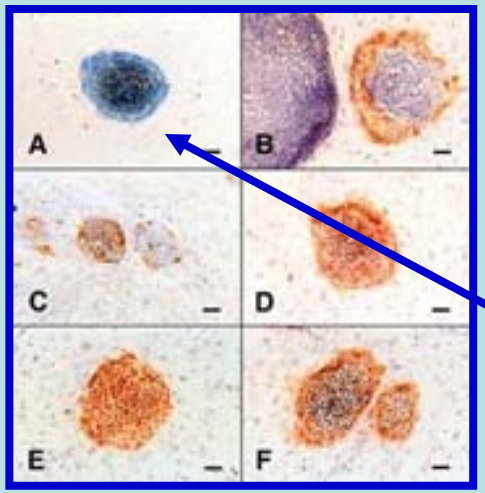
Roberto F. Vina Design



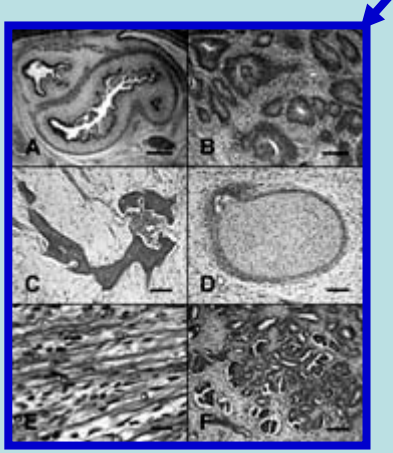
Cell Analysis

- **Cell number**
- **Cell viability**
- **Microbiology??????**
- **Cell contents**
- **Cell purity**

Stems Cells Procedure Isolation



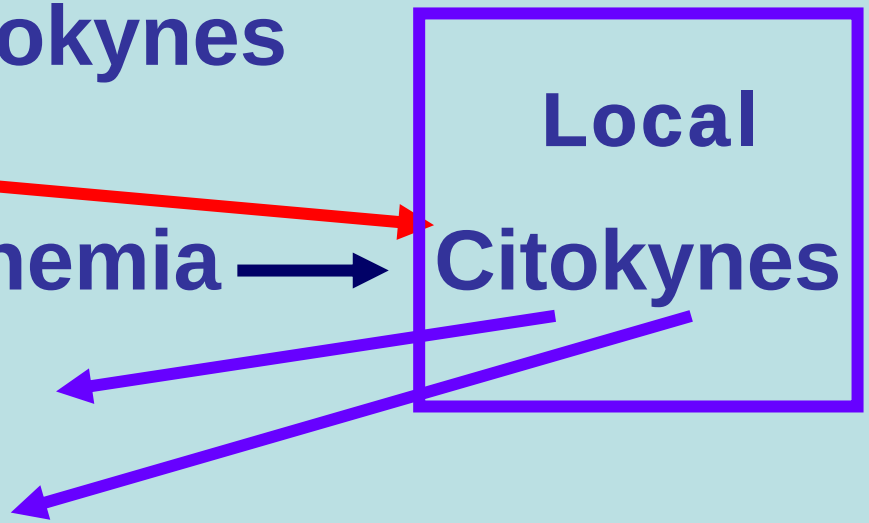
The average of Mononuclears Cells obtained was 569 x 10 p6, the average of cells with CD 34 (+)marked was 22,5 x 10p6 and the average of mononuclears cells with CD34(+) & CD38(-) was 3,07 x 10p6.



Fundación
Don Roberto
Fernandez Viña

Play Rules

- To repair we need>>>>>>>>>>>>
- Not Only Cells …
- We need also >>>>>>>>>
- General Body Citokynes
- Inflamation
- Muscle Heart Ischemia
- Cells mobilization
- Paracrine effects



Program of Implants & Cellular Therapy in Heart (TECELCOR) Argentina (February 2003)

Group I: Implant and Cellular Therapy in Myocardial Infarction
TECELCOR I

Group II: Treatment with Implant and Cellular Therapy of Patients with Chronic Myocardial Infarction with refractory angina (TECELCOR II Argentina Study),

Group III: Treatment with Implant and Cellular Therapy of Patients with Chronic Myocardial Infarction with refractory Cardiac Failure (TECELCOR III Argentine Study)

Group IV: Pacient WITH Not Coronary Míocardiopathy
TECELCOR IV

Fundación Don Roberto Fernandez Viña

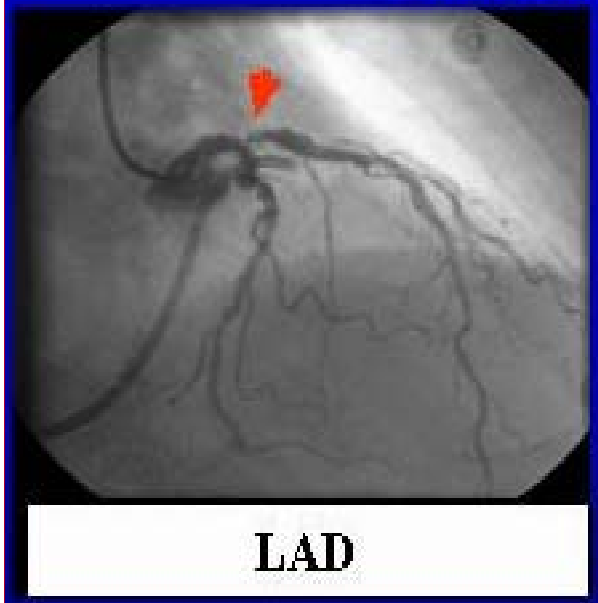
Implant throug Coronary Veins

ANGIOGENESIS: Trans (Coronary) Venous Implantation Of Stems Cells In Chronic Coronary Disease
May 27, 2003

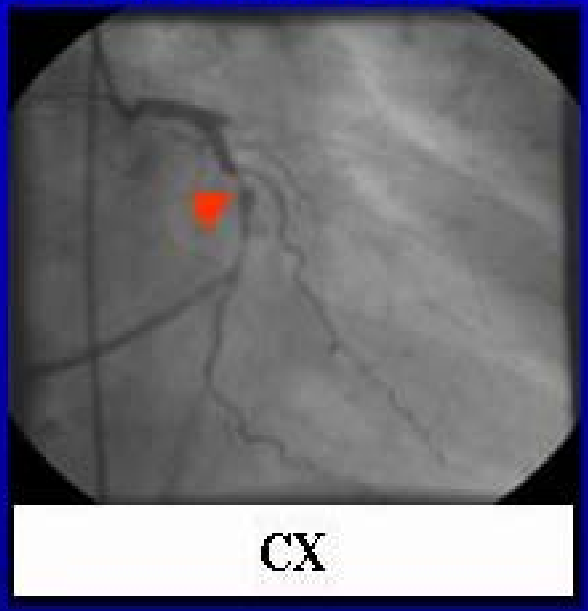
by R. Fernandez Vina

Operators:
Roberto Fernãndez Viña(1)(6), Saslavsky Jorge(2)(6), Vrsalovick Francisco(1), Nestor Muttis(1), Andrin Oberdan(1), Benetti Federico(3), Geffner Luis(3), Amit Pathel(4), Diez Juan(7)(6), Dlugovitzky Diana(8), Fernãndez Vina Marcelo

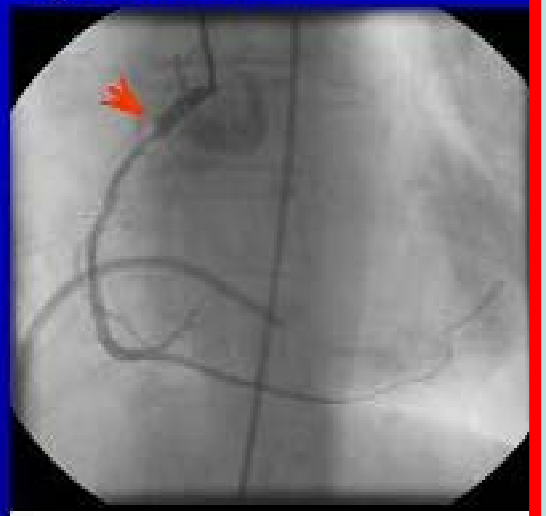
Selective Retroinfusion of Coronary Veins



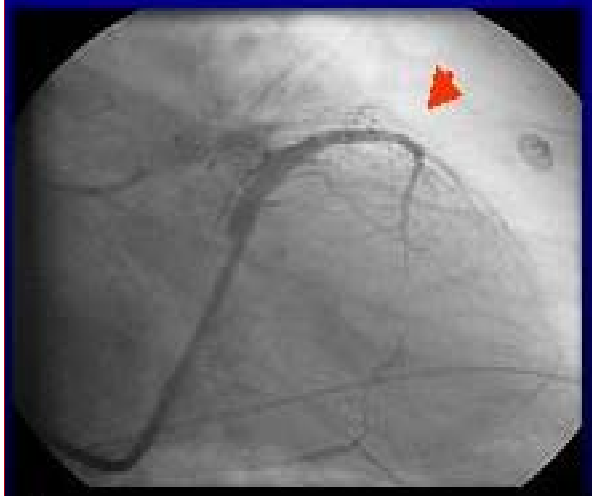
LAD



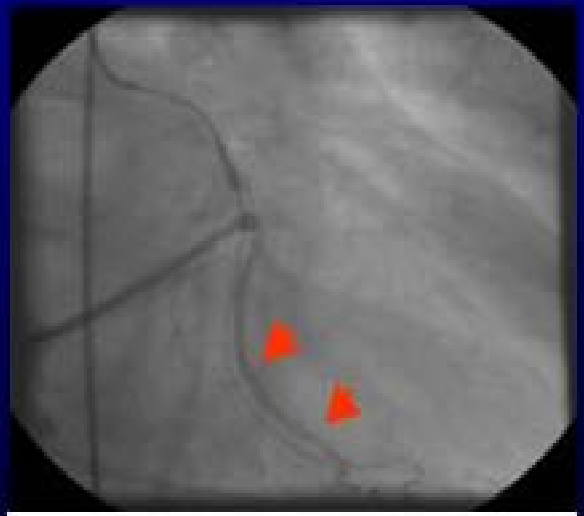
CX



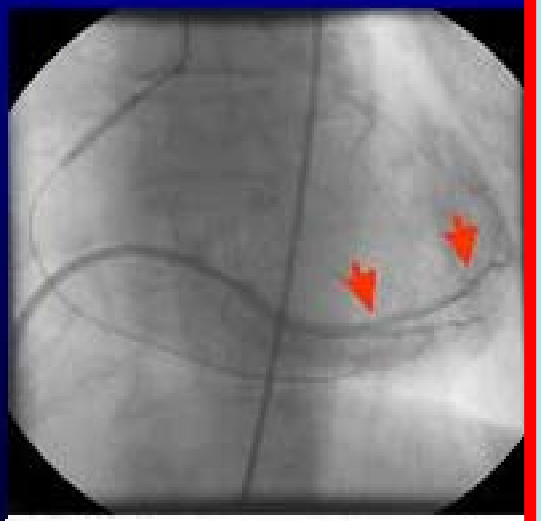
RCA



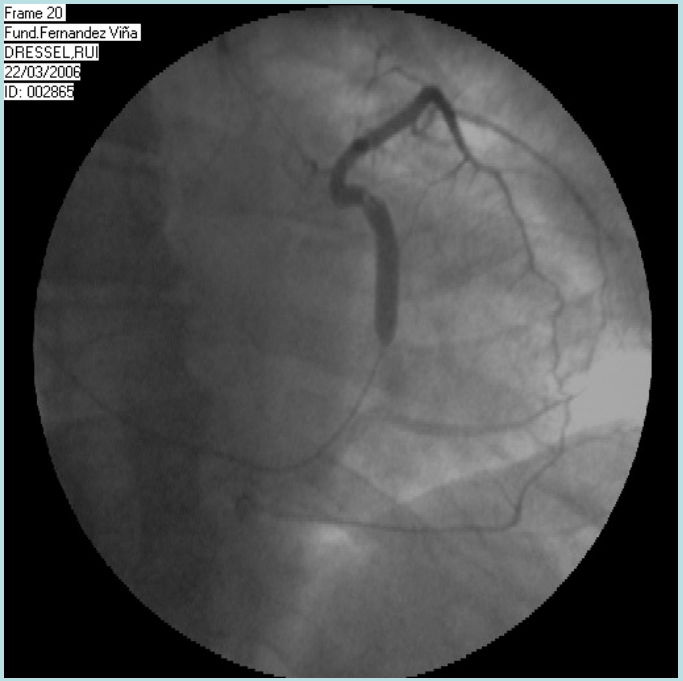
Anterior cardiac vein



CX Vein



RC Vein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Fund.Fernandez Viña
DRESSEL,RUI
22/03/2006
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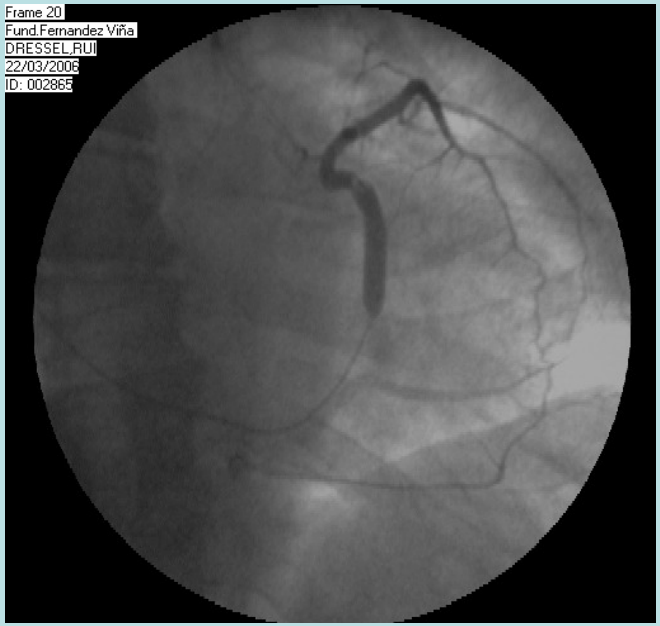
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DRESSEL,RUI
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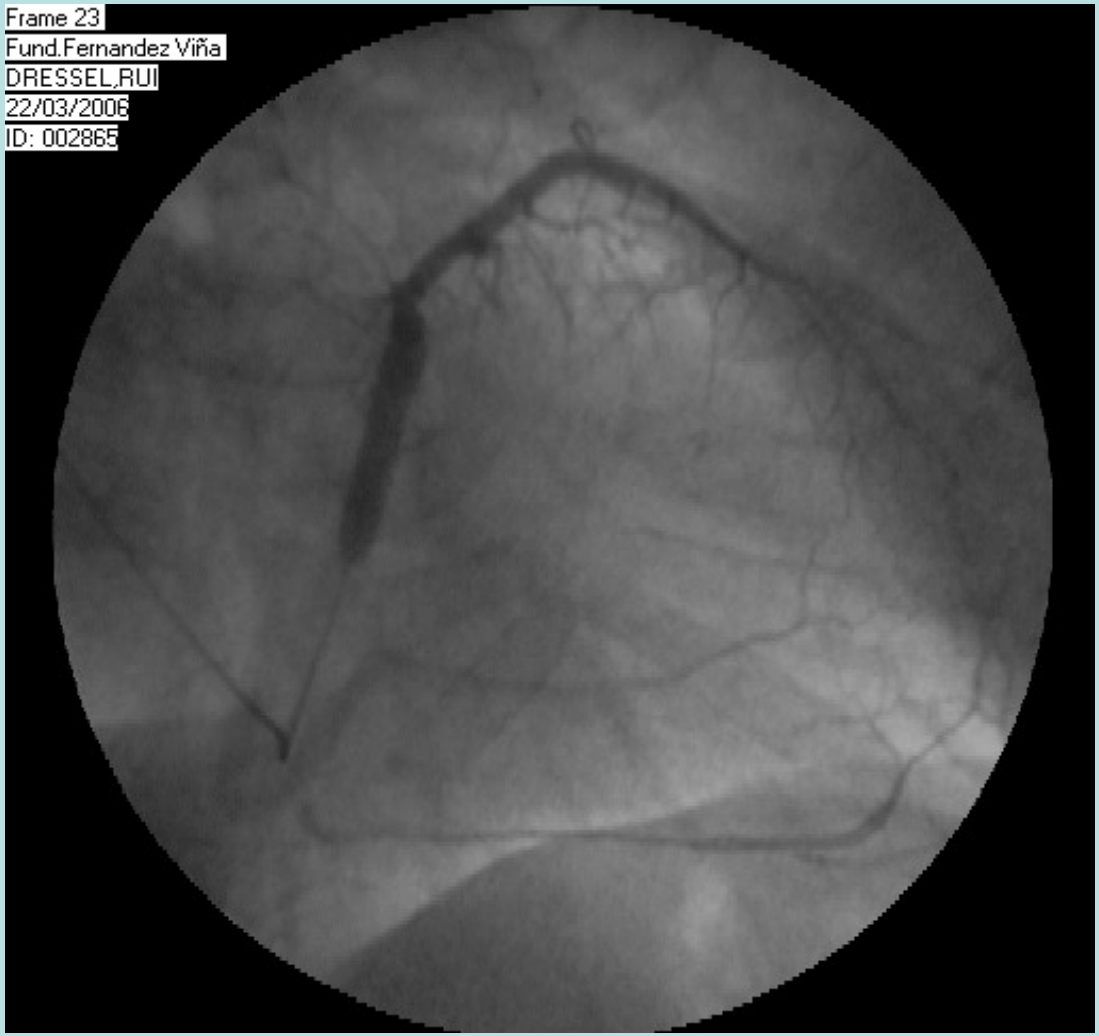
Frame 23
Fund.Fernandez Viña
DRESSEL,RUI
22/03/2006
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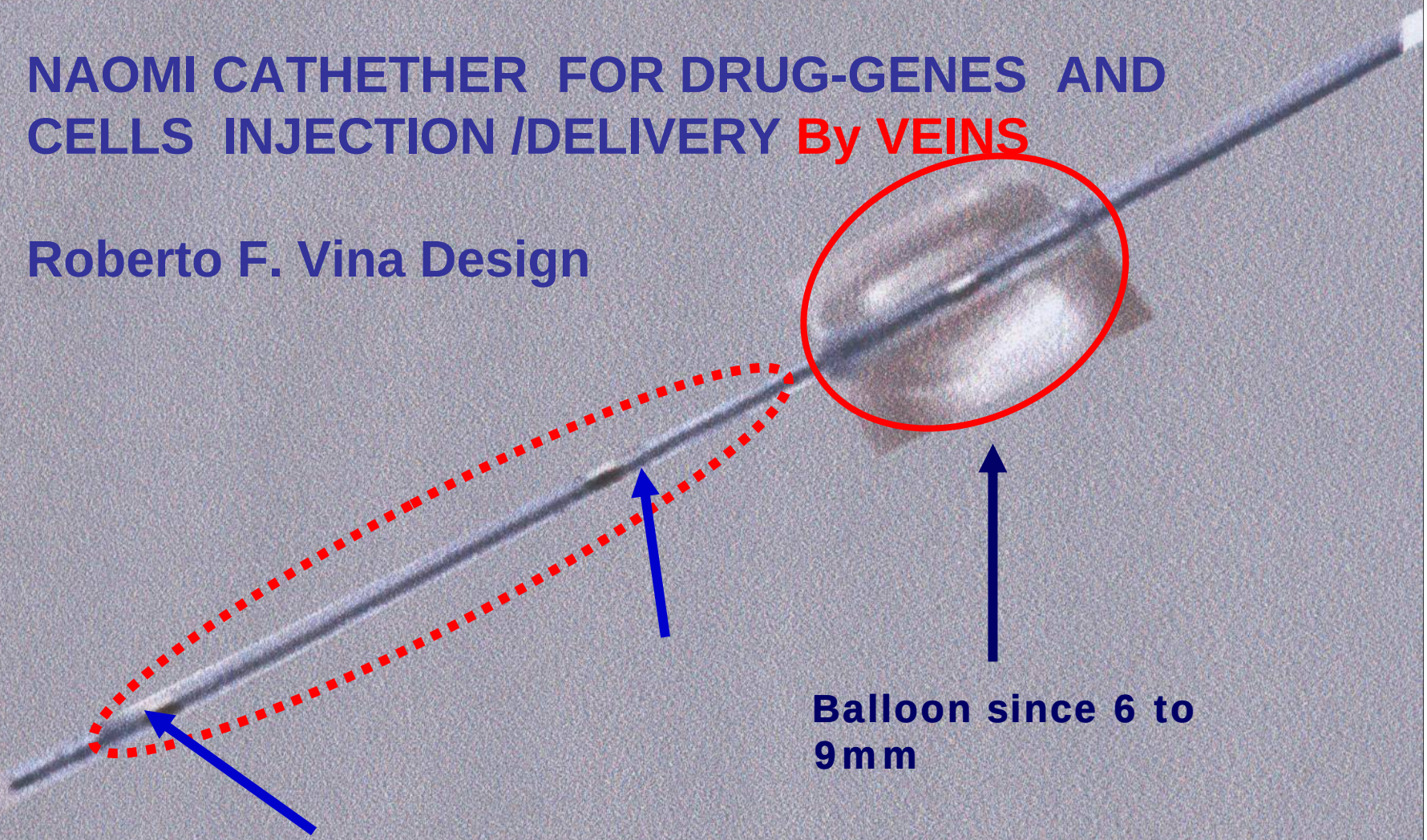
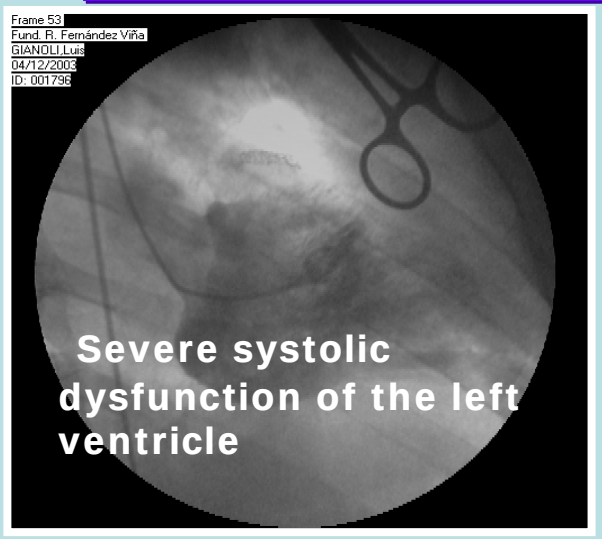
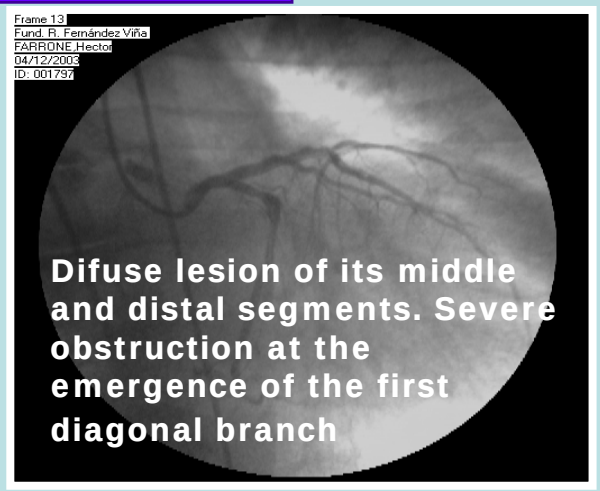
NAOMI CATHETHER FOR DRUG-GENES AND CELLS INJECTION /DELIVERY By VEINS

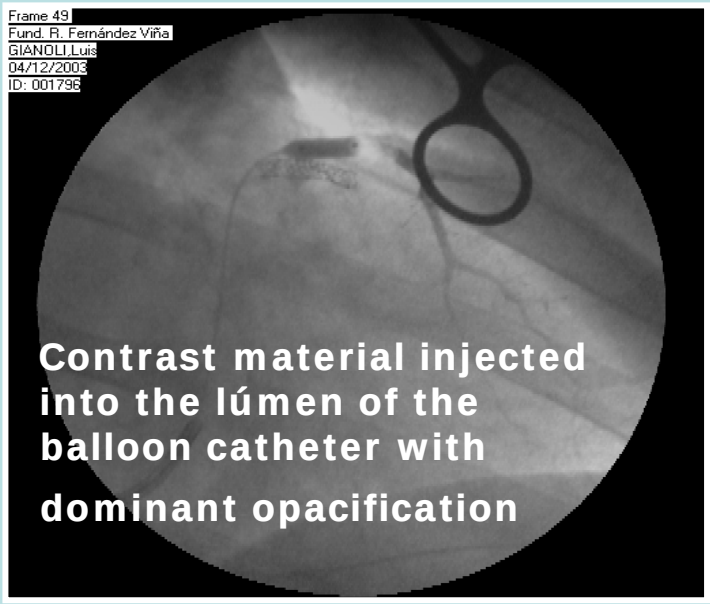
Roberto F. Vina Design

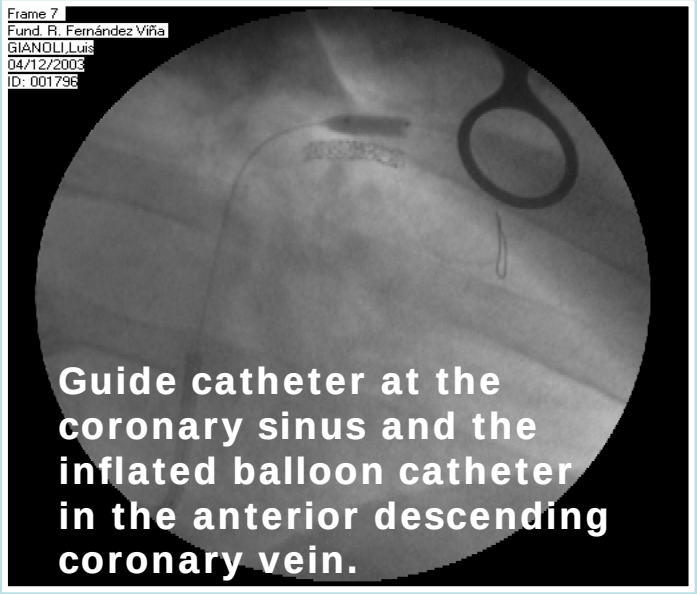


Retrograde veined Injection









From Bench to Bedside

- **Three years follow up of Cellular Therapy treatment of Patients with Chronic Coronary Disease with angina or cardiac failure and not options of surgical revascularization**

- ***#110 patients with refractory angina or cardiac failure and no possibility of surgical revascularization were included.***
- ***Age of patients oscillated between 43 and 81 years old.***
- ***Sex:96 men and 14 women***

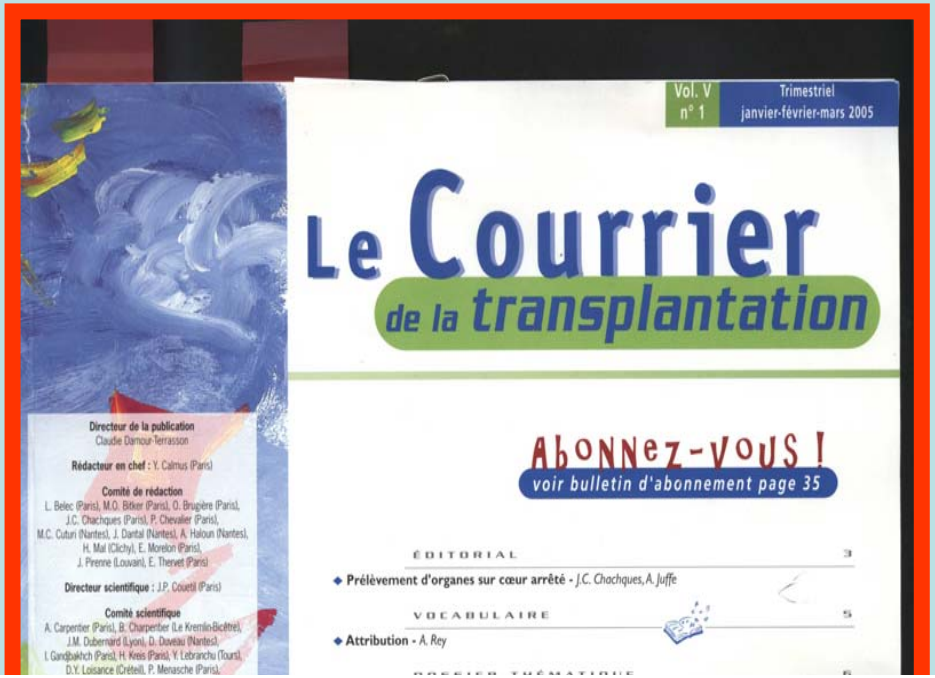
- **Ventriculography revealed a deterioration of the contractile function in all the patients with increase of the End Diastole Volumes and end of Systole volumes, with Fractions Ejections that oscillated between 22% and 38%.**

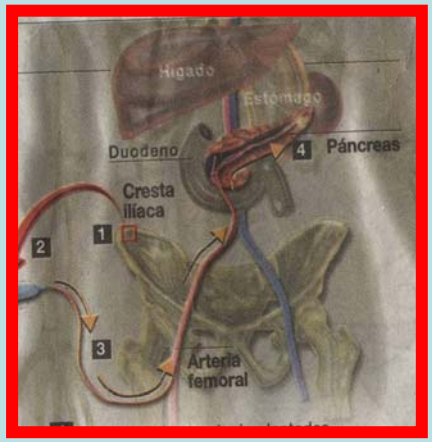
.

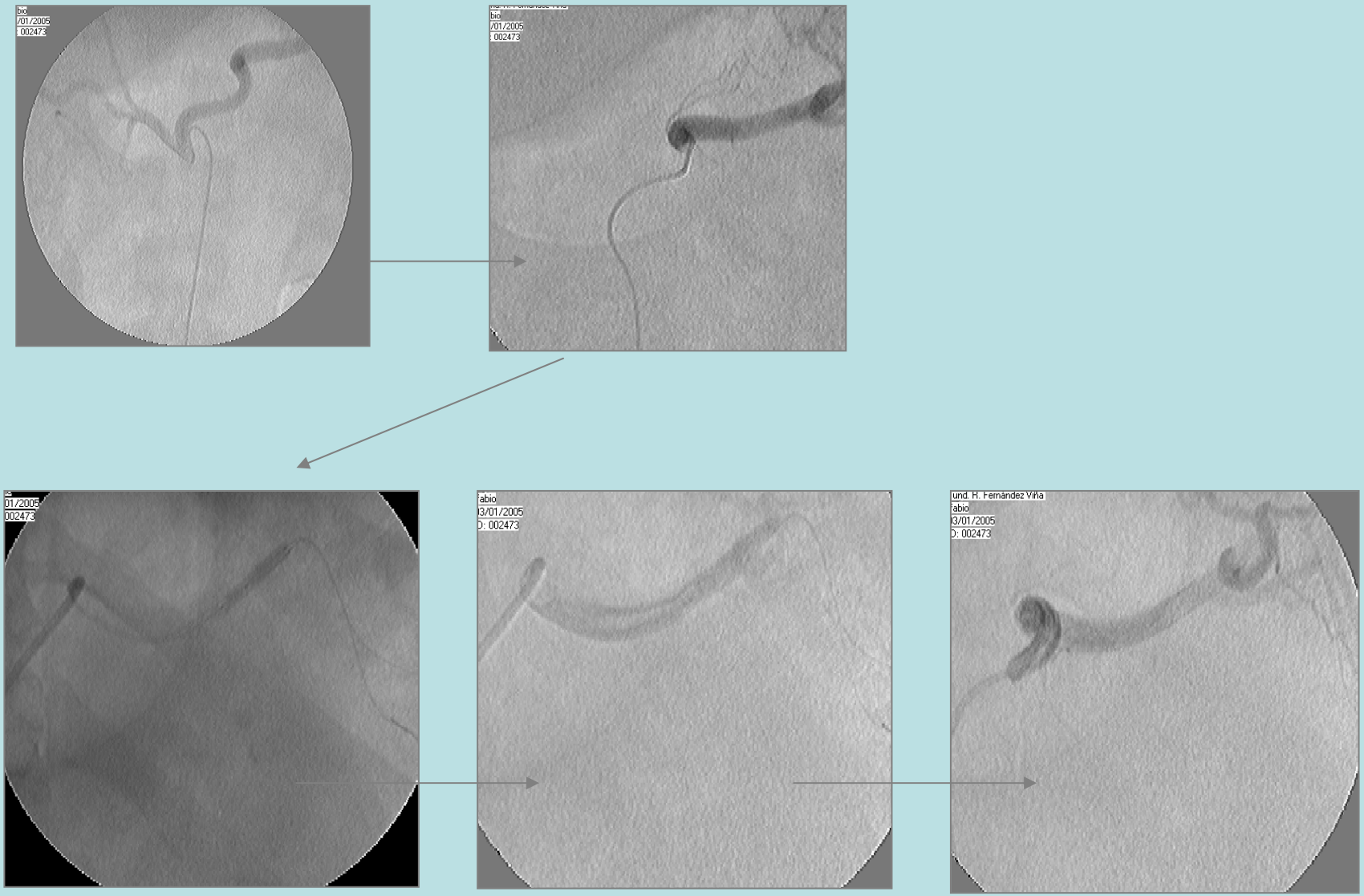
Follow up:

- *After a period of three month a progressive increase of sectors contractility was observed in the* ***echocardiograms.***
- *After 180 days it was observed that FE had improved between* ***36% and 41%.***
- ***Scintigraphy*** *controls revealed improvement of the perfusion in the 83 patients in the perinecrótic and diffuse ischemic areas,*
- *68 patients were subjected to* ***ventriculography*** *after 360 to 900days and it was observed that the FE* ***improved up to 38%.***

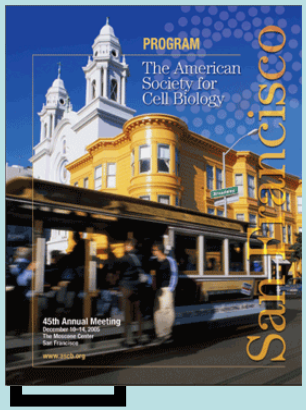
***First World Report -from Argentina- on the Feasibility of the Implant of Autologous Stem Cells with an Endovascular Technique, in a Diabetes Mellitus Patient* 2 January 2005**







First Reported Datas from Argentina of Implant and Cellular Therapy in patients with type 2 diabetes (TECELDIAB Study I)



Fundación Don Roberto Fernandez Viña

Type 1 Diabetics Patients Evolution and Results First word report after adult stems cells implant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