

# Stem Cell Injection in Surgical Management of Ischemic Heart Patients with Non-Contractile or Ungraftable Cardiac Segments

### Thesis

Submitted for Partial Fulfillment of a MD in Cardiothoracic Surgery

### Presented by

#### **Motaz Sobhi Ahmad Rabie**

Master Degree in General Surgery-Ain Shams University

## Under Supervision of

## Prof. Dr. Mohammed Magdy Mostafa

Professor of Cardiothoracic Surgery Faculty of Medicine - Ain Shams University

### Prof. Dr. Alaa Ismail Abdel-Mottaleb

Professor of General Surgery Faculty of Medicine - Ain Shams University

# Prof. Dr. Mohammed Mohammed El-Fiky

Professor of Cardiothoracic Surgery Faculty of Medicine - Ain Shams University

### **Dr. Ayman Mahmoud Ammar**

Professor of Cardiothoracic Surgery Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
2012

# إستخدام الحقن الجراحي للخلايا الجذعية لعلاج مرضى قصور الشرايين التاجية

رسالة

توطئة للمصول على درجة الدكتوراة في جراحة القلب والصدر

مقدمة من

الطبيب/ معتر صبحي ربيع ماجيستير الجراحة العامة ـ كلية الطب جامعة عين شمس

تح**ت إشراف** الائستاذ الدكتور/ محمد مجدى مصطفى

كلية الطب- جامعة عين شمس

الائستاذ الدكتور/علاء اسماعيل عبد المطلب

كلية الطب- جامعة عين شمس

الائستاذ الدكتور/ محمد محمد الفقى

كلية الطب- جامعة عين شمس

الدكتور/ أيمن محمود عمار

كلية الطب جامعة عين شمس

كلية الطبب جامعة عين شمس ٢٠١٢



First of all, thanks to **Allah** who granted me the ability to accomplish this work.

I would like to express my deepest and utmost thanks to **Prof. Dr. Mohammed Magdy Mostafa**, Professor of Cardiothoracic Surgery for his sincere guidance, kind supervision and great help. I was honored to be his candidate and to be guided all through this work by his kind and valuable advices. You've always been like a father to all of us, thank you so much.

I wish also to express my great gratitude and utmost appreciation to **Prof. Dr. Alaa Ismail Abdel-Mottaleb**, Professor of General Surgery, for his valuable participation and instructions. The whole idea of this study started when I listened to one of his lectures & was impressed by the way he believes in his work. There is always a lot to be learnt from you, thank you so much.

I wish also to express my great appreciation to **Prof. Dr.**Mohammed Mohammed El-Jiky, Professor of Cardiothoracic Surgery, for his efforts. Since day one, your guidance & instructions have been the main factor for this study to end by the way it looks today, thank you so much.

Also, I would like to express my appreciation to **Prof. Dr. Ayman Mahmoud Ammar**, Assistant Professor of Cardiothoracic Surgery, for his sincere advice and his open-mind. Your support and help in solving any problem facing me during the progress of this work would never be fogetten, thank you so much.

I must also dedicate this work to the following professors for their valuable participation in this study. I will never forget your efforts that helped this study to become a reality.

### Cardiothoracic Surgery department:

**Prof. Dr. Ezz El-Dien Mostafa**, for being so understanding & supportive.

**Prof. Dr. Ahmad Hassouna**, for being so generous in giving his effort & time to help in the statistics & results of this study.

**Prof. Dr. Ahmad El-kerdany**, for taking care of all of us. You are a kind of persons who *LOVES* to help others.

Prof. Dr. Tarek El-Sayegh, for his participation in the study.

Prof. Dr. Walaa Saber, for his particiration in the study.

**Prof. Dr. Mostafa Abdel-Azim**, for his participation in the study.

Prof. Dr. Saeed Refaat, for his particiration in the study.

### Cardiology department:

**Prof. Dr. Zeinab Abdel-Salam**, for being supportive & flexible in performing Dobutamine stress echocardiography for the whole 31 patients included in this study.

### Radiology department:

**Prof. Dr. Waheed Tantawy**, a great professor & a great person as well who finds happiness in helping others, it was my pleasure to deal with him *before* & throughout the study.

**Prof. Dr. Ahmad Samir**, for being so skillful, helpful & devoted, you never hesitate to do all the best for patients.

I was honored that our cases included in this study were some of the first cases in all Egypt that had cardiac MRI done. Thank you both for giving me this chance.

Finally, I would like to thank **Mr. Ali Abdel-Bar** for his help, not only as the provider of *Harvest Technologies Kits* & the centrifugal system but also as a partner and above all as a friend.

I was lucky enough to work with such a great team....

Thank You All



In the beginning, I dedicate this work to my parents, the reason of any good thing that happened or would ever happen to me. Any achievement I had is mostly because of your help and endless prayers to me, thank you so much.

Second, I wish to thank my wife **Tr. Hala** for her generous help, support, effort, time, advice and wishes. Without you non of this would ever be done, thanks God for giving me the pleasure of having you in my life.

I also dedicate this work to my beautiful children Marwan, Yassin and Togine they are the real motive for every step I take. The world is really nice with you in it.

I must also dedicate this to my brothers who are always arround me whenever I need them. It always makes me feel safe & secured.

In fact, I am glad and proud to have this great family beside me. Without you, my life would be much more difficult.

God bless you all

# **List of Contents**

Title	Page
Introduction	1
Aim of the work	7
Review of Literature:	
Chapter (1): Ischemic Heart Disease with Non-Viable or Ungraftable Segments	9
Chapter (2): Introduction to Stem Cell Therapy	28
Chapter (3): Stem Cell Therapy in Ischemic Heart Disease	66
Patients and Methods	101
Results	120
Discussion	148
Summary	
Conclusion	
Limitations	181
Recommendations	182
Appendices	184
References	196
Arabic Summary	

## List of abbreviations

ABMMNCs Autologus Bone Marrow Mononuclear Cells

AECs Amniotic epithelial cells

AMI Acute Myocardial Infarction

BLI bio-luminescence imaging

BM Bone Marrow

BMCs Bone marrow derived cells

CABG Coronary Artery Bypass Grafting

CAC Canadian angina classification

CAD Coronary Artery Disease

CCU Coronary Care Unit

CD Cluster of Differentiation

CMRI Cardiovascular magnetic resonance imaging

CSCs Resident cardiac stem cells

CT Cardiac computed tomography

DE Delayed Enhancement

DNMT3B DNA (cytosine-5-)-methyltransferase 3 beta

DSE Dobutamine stress echocardiography

EAPCs Endogenous adult stem/progenitor cells

EBAF Endometrial bleeding associated factor

EBs Embryoid bodies

EDD End Diastolic Diameter

EF Ejection Fraction

EPC Endothelial progenitor cells

ESCs Embryonic stem cells

ESD End Systolic Diameter

EuroSCORE European System

for Cardiac Operative Risk Evaluation

FACS Fluorescence activated cell sorting

FDG Fluorodeoxyglucose

FGF2 Fibroblast growth factor 2 protein

FSCs Fetal Stem Cells

G-CSF Granulocyte-colony-stimulating factor

HDF Human dermal fibroblasts

hES Human embryonic cells

HLA Human leucocyte antigen

HSCs Heamopoietic stem cells

IC Ischemic Cardiomyopathy

ICMs Inner cell masses

IGF-1 Insulin-like growth factor-1

IHD Ischemic Heart disease

iPS Induced pluripotent stem

LAD Left Anterior Descending Artery

LCX Left Circumflex

LIMA Left Internal Mammary Artery

LV Left ventricle

MEF Mouse embryonic fibroblasts

MHC Major histocompatability complex

MR Mitral regurge

MSC Mesenchymal stem cells

MVD Multivessel disease

NYHA class New York Heart Association Classification

Oct-4 Octamer-binding transcription factor 4

PBSCs Peripheral blood stem cells

PCI Percutaneous coronary intervention

PDA Posterior Descending Artery

PET scan Positron emission tomography

RCT Randomized Controlled Trial

SCID Severe Combined Immunodeficiency

SCNT Somatic cell nuclear transfer

SCs Stem Cells

SDF-1a Stromal cell-derived factor-1 alpha

SOX2 (sex determining region Y)-box 2

SPECT Single photon emission computed tomography

SSEA Stage-specific embryonic antigen

STS Society of Thoracic Surgeons mortality risk score

SVG Saphenous Venous Graft

SYNTAX SYNergy between PCI with TAXUS<sup>TM</sup> and

Cardiac Surgery

TGF Transforming growth factor beta

TMLR Transmyocardial laser revascularization

TRA Tumor-rejection antigen

TTE Transthoracic Echocardiography

UCB Umbilical cord blood

UCCs Umbilical cord cells

UCE Umbilical cord epithelium

# **List of Figures**

Fig. No.	Title	Page No.	
	Figures in Review of Literature		
1	Schematic diagram depicting the principle definitions of stem cells; self renewal through replication, and differentiation into tissue-specific cell lineages.	30	
2	Stem cell division and differentiation.	32	
3	Examples of plasticity of somatic stem cells or stem/progenitor cells isolated from specific organs as determined by their ability to differentiate into different tissue-specific phenotypes when transplanted into different organs.	42	
4	Distinguishing differentiation from fusion by cytogenetic analysis based on the identification of sex chromosomes e.g. in hepatocytes.	43	
5	Schematic diagram showing the possible differentiation pathways of ESCs.	48	
6	Scheme showing the tissues/organs constituting the potent targets for tissue regeneration by stem cell-based therapies.	61	
Figures in Results			
1	Illustration of a comparison between pre- operative and post- operative NYHA, EF & maximum EF in post- operative DSE in group (A) patients.	124	

2	Illustration of a comparison between pre- operative and post- operative NYHA, EF & maximum EF in post- operative DSE in group (B) patients.	125
3	Illustration of a comparison between pre- operative and post- operative EDD& ESD in group patients (A).	127
4	Illustration of a comparison between pre- operative and post- operative EDD& ESD in group patients (B).	129

## **List of Tables**

Tables No.	Title	Page No.	
	Tables in Review of Literature		
1	Classical view of somatic cells regarding lineage potential and repopulation capacity.	33	
	Figures in Results		
1	Descriptive Statistics of all patients included in both groups.	121	
2	Pre- operative risk factors in all patients included in both groups.	122	
3	Percentage of mitral valve repair among the included patients.	123	
4	Comparisons between pre- operative and post- operative NYHA, EF & maximum EF in post- operative DSE in group (A) patients.	124	
5	Comparisons between pre- operative and post- operative NYHA, EF & maximum EF in post- operative DSE in group (B) patients.	125	
6	Comparisons between pre- operative and post- operative EDD& ESD in group patients (A).	126	
7	Comparisons between pre- operative and post- operative EDD& ESD in group (B) patients.	128	
8	Comparing akinesia in pre- operative and post- operative echocardiography in group (A) patients.	130	

9	Comparing akinesia in pre- operative and post- operative echocardiography in group (B) patients.	131
10	Comparing viability in pre- operative and post- operative Dobutamine stress echocardiography in group (A) patients.	132
11	Comparing viability in pre- operative and post- operative Dobutamine stress echocardiography in group (B) patients.	133
12	Induced ischemia in post- operative Dobutamine stress echocardiography. Comparison between group A & group B.	134
13	Percentage of mitral valve repair among the included patients.	135
14	Comparing significant mitral regurge in pre- operative and post- operative Dobutamine stress echocardiography in group (A) patients.	136
15	Comparing significant mitral regurge in pre- operative and post- operative Dobutamine stress echocardiography in group (B) patients.	137
16	The mean number of lesions & grafts in both groups.	138
17	Correlation between viability in post- operative Dobutamine stress echocardiography and CABG with 3 grafts or more in group A patients.	139
18	Correlation between viability in post- operative Dobutamine stress echocardiography and CABG with 3 grafts or more in group B patients.	140