DOI:10.1111/j.1540-8175.2008.00696.x

CellTherapyinPatientswithLeftVentricular DysfunctionDuetoMyocardialInfarction

RomanPanovsky,M.D.,Ph.D.,
JaroslavMeluzin,M.D.,Ph.D,F.E.S.C.,
StanislavJanousek,M.D.,Ph.D.,
Jiÿr«õMayer,M.D.,Ph.D.,
MilanKaminek,M.D.,Ph.D.,
LadislavGroch,M.D.,
Jiÿr«õPrasek,M.D.,Ph.D.,
JaroslavStanicek,M.D.,
LadislavDusek,
M.D.,#OtaHlinomaz,M.D.,Ph.D.,
PetrKala,M.D.,Ph.D.,
MartinKlabusay,M.D.,Ph.D.,
ZdenekKoristekM.D.,
andMilanNavratilM.D.
FirstDepartmentofInternalMedicine/Cardioangiology,St.AnnaHospital,Masaryk University,
Brno,CzechRepublic,
DepartmentofInternalMedicine/Cardiology,BrnoUniversityHospital,
Brno,CzechRepublic,
DepartmentofInternalMedicine/Hematooncology,BrnoUniversity Hospital,Brno,CzechRepublic,
DepartmentofNuclearMedicine,UHOlomouc,CzechRepublic,
DepartmentofNuclearMedicine,BrnoUniversityHospital,Brno,CzechRepublic,
DepartmentofNuclearMedicine,MasarykMemorialCancerInstitute,Brno,CzechRepublic,and#Centerof

BiostatisticsandAnalyses,BrnoUniversityHospital,Brno,CzechRepublic

Objectives:Thepurposeofthisstudywastodeterminetheimpactofautologoustransplantation
ofmononuclearbonemarrowcellsonmyocardialfunctioninpatientswithleftventricular(LV)

dysfunctionduetoanacutemyocardialinfarction.Methods:Therandomizedstudyincluded82

patientswithaÞrstacutemyocardialinfarctiontreatedwithastentimplantation.Thispresentation

isasubanalysisof47patientswithleftventriculardysfunctionÐEF(ejectionfraction)
40%.Group
Hpatients(n
17)receivedhighernumber(100,000,000)ofcells;GroupLpatients(n
13)received
lowernumber(10,000,000)ofcells.ThepatientsofcontrolGroupC(n
17)werenottreatedwith
cells.TheDoppler tissueimagingandsinglephotonemissioncomputedtomographywereperformed

beforecelltransplantationand3monthslater.Results:At3monthsoffollow-
up,thebaselineEF

of35%,36%,35%inGroupsH,L,andCincreasedby6%(P
0.01vs.baseline),5%(P
0.01vs.
baseline),and4%(P
NSvs.baseline),respectively,asassessedbysinglephotonemissioncomputed
tomography(P
NSbetweengroups).Thebaselinenumberofakineticsegmentsof6.9,7.0,and6.2in
H,L,andCgroupsdecreasedby1.7(P
0.01vs.baseline),1.5(P
0.01vs.baseline),and0.7(P
NSvs.baseline,P
NSbetweengroups),respectively,asdemonstratedbyechocardiography.Conclusion
:
Inourstudy,thestatisticallyimportanteffectoftransplantationofmononuclearb
onemarrowcells

onmyocardialfunctionwasnotfound.Onlyaninsigniþcanttrendtowardtheimproveme
ntofglobal

LVEFfractionwasfoundat3-monthfollow-
up.(ECHOCARDIOGRAPHY,Volume25,September

2008)stemcells
,coronaryarterydisease
,leftventriculardysfunction
Postmyocardialinfarctioncongestiveheart
failureremainstobeamajorclinicalprob-

lem,despiteadvancesinthemedicalandsur-
Theworkwassupportedinpartbyagrantoftheministry
ofHealthoftheCzechRepublic(IGA,No.1A/8676-3),and

bygrantsoftheMinistryofEducationoftheCzechRepublic

(MSM,No.0021622402andMSM,No.0021622430).Oth-

erwise,thereisnoconßictofinterest.
Addressforcorrespondenceandreprintrequests:Ro-
manPanovsk
«y,Ph.D.,FirstDepartmentofInternal
Medicine/Cardioangiology,St.AnnaÕsHospital,Masaryk

University,Peka
ÿrsk«a5365691Brno,CzechRepublic.Fax:
420-543182205;E-mail:panovsky@fnusa.cz
gicaltreatmentofacutecoronarysyndromes.
Coronaryarterydiseaseaccountsforapprox-

imately50%ofallcardiovasculardeathsand

istheleadingcauseofcongestiveheartfail-

ure.The1-yearmortalityrateforpatientsdi-

agnosedwithcongestiveheartfailureisabout

20%,andfrom1994to2004,deathsfromheart

failureincreased28%.
12Developmentofheart
failureinsurvivorsofacutemyocardialinfarc-

tioninvolvesmyocytelossintheareasupplied

bytheinfarct-relatedarteryandsubsequent

formationofnoncontractileÞbroustissue.To

date,notherapeuticprocedurelikeangio-

plastyorthrombolyticagentscouldreversethe

---

irreversiblemyocardialinjurycompletely.The
recoveryofcontractilefunctionafterrevascu-

larizationoccursonlyintheareasofhibernat-

ingmyocardium.Hearttransplantationmaybe

anoptioninselectedpatients,butthedonor

supplyisstrictlylimited.
Recentexperimentalandclinicalstudiessug-
gestthatcelltransplantationintodamagedmy-

ocardiummayhavethepotentialtorestore

myocardialviabilityandimproveleftventric-

ularfunction.Differentcelltypescanbepo-

tentiallyusedfortransplantation.Toavoid

problemswithdonoravailability,immunolog-

icalrejection,arrhythmias,andethicalprob-

lems,autologousbonemarrowcellsappearpar-

ticularlyattractive.Butinamajorityofstudies,

onlypatientswithalmostnormalfunctionor

onlymilddysfunctionoftheleftventriclewere

studied.3Ð12Sothepurposeofthisstudywastodetermine
theimpactofautologoustransplantationof

mononuclearbonemarrowcellsonmyocardial

functioninpatientswithmoderate-to-severe

leftventriculardysfunction.
MaterialsandMethods
StudyPopulation
Therandomizedstudyincludedpatientswith
aÞrstacutemyocardialinfarctiontreatedwith
coronaryangioplastywithastentimplanta-

tion.Onlypatientswithsuccessfulrecanaliza-

tionoftheinfarct-relatedartery(TIMI
ßowgrade3)andtheevidenceofanirreversible

damageofatleasttwoakineticordyskinetic

myocardialsegmentsidenti
Þedbydobutamine
echocardiography,gatedtechnetium-99mses-

tamibisinglephotonemissioncomputedto-

mography,andpositronemissiontomography

(performedinonly73%ofpatients)werein-

cluded.Theexclusioncriteriawere:(1)age
70years;(2)noncardiacdiseaseadverselyaf-

fectingprognosis;(3)anothercardiacdisease

exceptcoronaryarterydisease;(4)coagulopa-

thy,thrombocytopenia,leucopenia;(5)absence

ofasigni
Þcantincreaseincardiacenzymes(cre-
atinekinaseover20
kat/lorcreatinekinase-
MBover3
kat/lortroponinIover20
g/l–Ðnormalupperlimitsinourlaboratoriesare
2.85kat/l,0.42
kat/l,and2.0
g/l,respec-
tively);(6)patientinstabilityondays3
Ð7after
MI;and(7)needforcoronaryrevascularization

inthefutureformultivesseldisease.
Fromatotalnumberof82patientswhocom-
pletedthebaselineand3-monthfollow-upex-
amination,66patientswereanalyzedinthe
previouslypublishedstudy.
12ThisÞrst66pa-
tientswererandomizedintothreearms:(1)a

grouptreatedwithahighernumberofmononu-

clearbonemarrowcells(de
Þnedasamean
numberof1
108cells);(2)agrouptreated
withalowernumberofcells(de
Þnedasa
meannumberof1
107cells);and(3)acon-
trolgroupnottreatedwithcelltransplanta-

tion.Subsequent16patientswererandomized

intoonlytwoarms:higher-dose-treatedgroup

andcontrolgroup.Thereasonforchangingran-

domizationschemawasnosigni
Þcanteffectof
alower-dosecellsinthepreviousstudy.This

presentationisasubanalysisof47(fromall

the82)patientswithsigni
Þcantleftventricu-
lardysfunction-
Ðejectionfraction(EF)
40%.Forty-
Þvepatientsunderwenttheprimaryan-
gioplasty(within12hoursofchestpainon-

set)andtwopatientsweretreatedwithangio-

plastywithintheintervalfrom12hoursto

3daysaftersymptomonset.
StudyDesign
Onday3
Ð6aftermyocardialinfarction,rest
anddobutamineechocardiographywasper-

formedtoevaluatethepresenceofakineticor

dyskineticleftventricularsegmentswithout

anycontractilereserve.Atthesametimecolor

Dopplertissueimagingwasperformed.Within

thenext2dayspatientsunderwentthegated

technetium-99msestamibisinglephotonemis-

sioncomputedtomographyandpositronemis-

siontomography.Patientswithanevidenceof

anirreversibledamageofatleasttwoakinetic

ordyskineticmyocardialsegmentsprovedby

allmethodswerethenrandomized.Patients

ofcellgroupsunderwentsubsequentlyabone

marrowaspiration.Autologousbonemarrow

mononuclearcellsweretransplantedintothe

infarct-relatedartery20
Ð21hoursafterthe
bonemarrowaspiration,5
Ð9daysaftermy-
ocardialinfarction.Immediatelybeforeand10

and20hoursaftertheprocedure,bloodsamples

forcardiacenzymes(creatinekinase,creatine

kinaseÐMBandtroponinI)wereacquired.
Threemonthsafterrandomization,rest
echocardiographywithDopplertissueimaging,

singlephotonemissioncomputedtomography,

andcoronaryangiographywererepeated.Pa-

tientsofthecontrolgroupunderwentthesame

proceduresandexaminations,asdidthetrans-

plantedpatientsexceptforbonemarrowaspi-

rationandcelltransplantation.

Inthissubanalysis,thechangesoffollowing
echocardiographicparameterswereassessed:

(1)thepeaksystolicvelocityofthemyocardium

adjacenttomitralannulusofinfarctedwall

(Sinfarct)(asaparameteroftheregionallongi-
tudinalleftventricularsystolicfunction);(2)

themeansix-sitesystolicvelocityofthemy-

ocardiumadjacenttomitralannulus(asapa-

rameterofthegloballongitudinalleftventric-

ularsystolicfunction),whichwascalculatedas

meansix-siteS
(SlateralSseptalSanteriorSinferiorSanteroseptalSposterior)/6;and(3)num-
berofakineticsegments.
Thechangesoffollowingparametersderived
fromsinglephotonemissioncomputedtomog-

raphywereassessed:(1)leftventricleend-

diastolicvolume;(2)leftventricleend-systolic

volume;(3)leftventricleejectionfraction;and

(4)perfusiondefectsize.
Theinstitutionalethicscommitteeapproved
thestudyandwrittenconsentwasobtained

fromeachpatient.
Echocardiography
Usingcommerciallyavailableequipment
Vivid7(GE/Vingmed,Milwaukee,WI,USA)

withanM3Stransducer,echocardiographicex-

aminationswereperformedinonecenter.Two-

dimensionalandcolorDopplertissueimagesof

apicalviews(apical4-and2-chamberandapi-

callong-axisviews)wereobtainedandstored

digitallyforthesubsequentof
ßinequantitative
analysisusingasoftwareincorporatedinVivid

7(Echopac7version1.3,GE/Vingmed).The

wider-anglesector(60
Ð70degrees)wasusedto
depicttwo-dimensionalimagesforwallmotion

analysis.Thenarrowanglesector(30
Ð45de-
grees)wasusedtoobtaincolorDopplertissue

imagesofindividualleftventricularwalls(sep-

tum,lateral,inferior,anterior,posterior,and

anteroseptalwalls)atthehighframeratesof

172Ð234framespersecond.
Dobutamineechocardiographywasper-
formedinallpatientswithstartingdoseof

5g/kgpermin.Thedosewasincreasedat

5-minuteintervalsto10,and20
g/kgper
min.Theparasternallong-axisandthree

apicalviewsweredigitallystoredatrestand

atthelastminuteofalldosesofdobutamine

forasubsequentwallmotionanalysis.A

16-segmentmodelwasusedforregionalwall

motionanalysis.
13Theakineticanddyskinetic
segmentswithnoimprovementinthickening

afteranydoseofdobutaminewereregarded

asirreversiblydamaged.Agoodinterobserver
andintraobservervariabilityinscoringdys-
functionalsegments(agreement93%and96%,

respectively)andindeterminingthecontractile

reserve(agreement92%and95%,respectively)

hasalreadybeendescribed.
14Theregionallongitudinalsystolicfunction
wasevaluatedfromthecolorDopplertis-

sueimaging.
1516Peaksystolicvelocities(S)
weredeterminedforthebasalmyocardium

ofeachwalladjacenttothemitralannulus

(Slateral,Sseptal,Santerior,Sinferior,Santeroseptal,and
Sposterior).Theresultswereobtainedasamean
fromthreeconsecutiveheartcycles.Twoexpe-

riencedechocardiographerswhowereblinded

tothepatienttreatmentperformedtheanaly-

ses.Thereproducibilityofestimationof Sval-

uesofindividualwallswasevaluatedinour

initial3-monthproject.
12ForallSvalues,the
estimated95%con
Þdencelimitsfordifferences
betweenintraobserver(JM)pairsofmeasure-

mentrevealedrepeatedresultstovaryina

rangeof
10.6%asbasedonthemeanprimary

valuesandsimilarly
11.5%fortheinterob-
servervariability(JMandRP).Thesuf
Þcientinterobserverreproducibilitywasalsoprovedin

appliedpairwiseANOVAmodels:only4.8%of

overallvariabilitycouldbeattributedtothedif-

ferencesamongobserversandtheinterobserver

effectwasunambiguouslynotsigni
Þcant(P
0.963).GatedTechnetium-99mSestamibiSingle
PhotonEmissionComputedTomography
SevenhundredfortyMBqtechnetium-99m
sestamibiwasinjectedatrest.Gatedsinglepho-

tonemissioncomputedtomographyimaging

acquisition(64projectionsfromthe45
rightanterioroblique projectiontothe45
leftpos-
terioroblique projection)began1hourafter

sestamibiinjectionusinga2-detectorgamma

camera(ecam,Siemens,Erlangen,Germany)

equippedwithalow-energy,high-resolution

parallel-holecollimators.TheMIBIuptake

wasanalyzedvisuallyandquantitativelyon

computer-generatedpolarmapsbyanexperi-

encednuclearcardiologistwhowasunaware

ofthepatientstreatment.Pixelswithases-

tamibiactivity
2.5SDbelowthecorrespond-
ingnormalmeanvalueswereconsideredab-

normal.Thecomputerautomaticallyexpressed

aperfusiondefectasthenumberofabnormal

pixelsdividedbythetotalnumberofleftven-

triclepixels
100project.
17Intheviability
analysis,themyocardialregionwiththemaxi-

mumsestamibiuptakewasusedasareference
890ECHOCARDIOGRAPHY:AJrnl.ofCVUltrasound&AlliedTech.

---

region.Thetraceruptakeinothermyocardial
regionswasthenexpressedasapercentage

oftheactivitymeasuredinthereferencere-

gion.Nonviablemyocardiumwasde
Þnedas
thathavingsestamibiuptakebelowthethresh-

oldof50%ofthemaximumproject.
18Gatedsinglephotonemissioncomputedtomography

restleftventricularejectionfractionsandleft

ventricularend-diastolic/end-systolicvolumes

wereobtainedusingautomated,commercially

availablesoftwarefour-dimensional-MSPECT

(UniversityofMichigan,AnnArbor,MI,USA).
PositronEmissionTomography
Toassessmyocardialviability,F-18-
ßuorodeoxyglucose-positronemissionto-
mographywasperformedwithawhole-body

positronemissiontomographyscanner(ECAT

ACCEL,Siemens,Knoxville,TN,USA).Ac-

quisitionwasstarted50minutesafterthe

administrationof
ßuorodeoxyglucose(200
Ð250MBqintravenously)andimagesofglucose

utilizationwereacquiredfor15
Ð20minutes
ina3Dmode.Themetabolicdefectswere

analyzedoncomputer-generatedpolarmaps.

Themyocardial
ßuorodeoxyglucoseuptakefor
eachpartoftheleftventriclewasnormalized

toamyocardialregionwiththemaximum

ßuorodeoxyglucoseuptake.Anonviablemy-
ocardiumwasde
Þnedasthathavingless
than50%ofthemaximum
ßuorodeoxyglucoseuptake.
18BoneMarrowAspirationandPreparation

Thetargetvolumeofbonemarrowblood (100mlforthelowercelldose,150mlfor thehighercelldose)wasobtainedfromiliac crestsunderlocalanesthesiaandmoderatese- dationwithmidazolam,mixedwith4%human albuminand5,000IUofheparin,andcen- trifuged(15minutes,240g)toreceivebuffy- coat.Mononuclearcellswerecollectedusing densitygradientcentrifugationofthebuffy- coat(20minutes,1,200g,Histopaque1077, Sigma-Aldrich,St.Louis,MO,USA),washed, andresuspended.Onehundredtwenty- Þveper- centofthetargetamountofmononuclearcells wasaddedtotheCellGroserum-freemedium (CellGenix,Freiburg,Germany)toreach0.3 Ð1.0106cells/ml.Afteranovernightcultiva- tion(37 C,5%CO2)inate ßonbag(VueLife, CellGenix),105%ofthetargetnumberof mononuclearcellswaswithdrawn,washed,and resuspendedintheHank Õssaltsolution(Sigma- Aldrich)with4%humanalbuminand1,000IU ofheparinintoatotalvolumeof22ml.

CellImplantation

Autologousmononuclearbonemarrowcells weretransplanted5 Ð9daysaftertheinfarc- tiononsetusingamodi Þcationofthemethod describedpreviouslybyStraueretal. 19Cellswereimplantedintracoronaryviaapercuta- neoustransluminalcatheterintotheinfarct- relatedcoronaryartery.Atotalofsevenballoon inßationsattheplaceofpreviousstentimplan- tationlastingfor3minuteswerecarriedout with3-minuteintervalsofballoonde ßation.At

thebeginningofeachballoonin
ßation,3ml
ofcellsuspensionwasslowlyinjectedintothe

artery.Allpatientswereondailydosesof75mg

ofclopidogreland100mgofaspirinand,inad-

dition,abolusof100units/kgofbodyweightof

heparinwasadministeredimmediatelybefore

theproceduretominimizetheriskofthrom-

boticcomplications.
StatisticalAnalysis
Standarddescriptivestatisticswereused
tosummarizethesampledistributionofin-

dividualvariables(means,standarderrors,

conÞdencelimits).Aunivariate
t-testfortwo
independentsampleswasappliedtocompare

valuesofparametersbetweenthegroups.A

pairedt-testwasappliedtocomparechanges
invaluespriorandafterthetreatment.All

parametrictestswereperformedwiththever-

iÞedassumptionofnormaldistribution
(ShapiroÐWilk
ÕsW-test).Twoindepen-
dentsamplesweremutuallycomparedon

thebasisofprovedhomogeneityofvariance

(VarianceratioF-test).Thecorrelationanalysis

wasbasedonPearson
Õscorrelationcoef
Þcient.AP0.05wasconsideredstatistically
signiÞcant.RepeatedmeasuresANOVAmodelwasused
totesttheresultsobtainedbydifferentob-

servers(measuredinallpatientsincluded

inthereproducibilitytest).Thepairwisede-

signincludedoverallF-testofthemainef-

fects(i.e.,differencesamongdifferentob-

servers)andthenestimationofwithin-observer

variability.

ResultsThissubanalysiscontains47patients.Thirty
ofthemweretreatedwithmononuclearbone

----------PANOVSKY,ETAL.
TABLEI
CharacteristicsoftheStudyPopulation
Control(C)LowerCellDose(L)HigherCellDose(H)
ParameterGroup(n
17)Group(n
13)Group(n
17)Age(years)52(2)55(2)55(5)
Men15(88%)12(92%)15(88%)

Hypertension9(53%)5(39%)5(29%)

Hyperlipidemia6(35%)9(69%)7(41%)

Diabetesmellitus4(24%)1(8%)3(18%)

Single-vesseldisease11(65%)9(69%)13(76%)

Double-vesseldisease6(35%)3(23%)4(24%)

Triple-vesseldisease0%1(8%)0%

IRA:LAD16(94%)12(92%)16(94%)

IRA:LCX0%0%0%

IRA:RCA1(6%)1(8%)1(6%)

MaximumCK(ukat/l)80.2(11.1)80.2(9.4)68.9(7.2)

MaximumCK-MB(ukat/l)7.4(0.6)7.6(0.9)6.8(0.7)

Timefrominfarctonsetto507(240)263(53)484(192)
reperfusion(min)
Timefrominfarctonsettocell
Ð7(0.4)7(0.3)
transplantation(days)
Dobutamineecho

No.ofirreversiblydamagedsegments6(0.7)7(0.4)7(0.7)

Medicationonhospitaldischarge
Aspirin17(100%)13(100%)17(100%)

Clopidogrel15(88%)13(100%)17(100%)

ACEinhibitor17(100%)13(100%)17(100%)

Betablocker17(100%)13(100%)17(100%)

Statin17(100%)13(100%)17(100%)

Thevaluesareexpressedasthemeansuppliedbystandarderror(inparentheses)ornumber(%)of
subjects.ACE
angiotensin-convertingenzyme;CK
creatinekinase;echo
echocardiography;IRA
infarct-relatedartery;LAD
leftanteriordescendingcoronaryartery;LCX
leftcircum
ßexartery;
Nonumber;RCA
rightcoronaryartery.
marrowcellimplantation
Ð17patientsinthe
GroupHwithhighercelldoses,while13in

theGroupLwithlowercelldoses,and17of

themservedasacontrolGroupC.Thebase-

linecharacteristicsarepresentedinTableI.

Therewerenosigni
Þcantdifferencesamongthe
groups.
TheEffectofCellTransplantation
onMyocardialFunctionandLeft

VentricleRemodeling
Theresultsofechocardiographicexamina-
tionsandsinglephotonemissioncomputedto-

mographydataaredemonstratedinTableII.
Therewasatrendtowardthepreventionof
theleftventricledilatation(end-diastolicvol-

ume)andtheimprovementoftheleftventri-

cleejectionfractionintransplantedpatients.

Patientsofthehigh-dosesgroupsigni
Þcantlyimprovedtheregionalsystolicfunction(S
infarct)after3-monthfollow-up.Weprovedsigni
Þcantimprovementintheseparameters(leftventri-
cleejectionfraction,end-systolicvolume,peak

systolicvelocityofinfarctedmyocardiumand

numberofakineticsegments)incelltherapy

patients,asitisdocumentedthroughsigni
Þ-cantresultsofwithin-grouptesting.However,

therewerenostatisticallydifferencesamong

thegroups.
Thesideeffectshavealreadybeenpub-
lished.12PhenotypeofTransplantedCells

Thesampleswereanalyzedfrom29patients
(inonepatientasmallsamplesizedidnotallow

adequateanalysis).Thetransplantedleuko-

cytescontainedinthemean43.4%CD3
cells,
2.9%CD16
cells,11.0%CD19
cells,0.4%
CD33cells,and1.1%CD34
cells,respec-
tively.Theviabilityofmononuclearcellswas

evaluatedafterthecultivation.Inallcases,the

viabilityexceeded95%.

TABLEII
ComparisonofBaselineand3-MonthFollow-
UpEchocardiographicandSinglePhotonEmissionComputedTomography
ResultsfortheTreatmentandControlGroups
MutualComparison(P-Values)
CGroupLGroupHGroup
Parameter(n
17)(n
13)(n
17)Cvs.LCvs.HLvs.H
Echocardiography
Mean6-siteS(cm/s)4.9(0.2)5.1(0.3)5.2(0.2)0.8210.4160.594

Baseline5.2(0.3)4.9(0.3)5.0(0.2)0.4850.6110.822

Follow-up0.3(0.2)
0.2(0.3)
0.2(0.2)0.2980.1530.813
Change0.3930.6250.193
P-valueSinfarct(cm/s)Baseline4.5(0.2)4.2(0.3)4.3(0.2)0.6910.9750.704

Follow-up4.8(0.3)4.4(0.3)4.7(0.3)0.2830.4320.728
Change0.3(0.2)0.2(0.2)0.4(0.1)0.2610.3420.215
P-value0.1530.3370.013
No.ofakinetics
Baseline6.2(0.6)7.0(0.4)6.9(0.6)0.3660.4110.889

Follow-up5.5(0.7)5.5(0.6)5.2(0.7)0.9950.7440.768
Change0.7(0.4)
1.5(0.5)
1.7(0.5)0.2420.1280.798
P-value0.0620.0010.001SPECTEDV(ml)171(9)176(12)178(13)0.7860.6770.907

Baseline183(13)180(12)181(12)0.8410.8760.957

Follow-up12(8)4(10)3(8)0.5090.4310.941

Change0.1530.6960.713
P-valueESV(ml)
Baseline112(7)112(9)117(10)0.9980.6740.694

Follow-up115(11)106(9)107(9)0.5550.5720.949
Change3(8)
6(7)
10(4)0.4020.0940.706
P-value0.7130.4080.023
LVEF(%)
Baseline35(1)36(1)35(1)0.3430.9390.308

Follow-up39(2)41(2)41(2)0.2840.3240.897
Change4(2)5(1)6(2)0.6090.2620.589
P-value0.0620.0010.001Perfusiondefect(%)
Baseline52(4)51(4)53(4)0.8800.9110.799

Follow-up41(4)41(5)43(4)0.8720.6570.800
Change11(3)
10(2)
10(2)0.6010.5370.958
P-
value0.0010.0010.001Thevaluesareexpressedasthemeansuppliedbystandarderror
(inparentheses).
IdentiÞedasnonviableonpretransplant
dobutamineechocardiography.
Mutualsigni
ÞcanceÒbetweengroups
Ótestedby
t-testfortwoindependentsamples.
Pairwise
calculatedÒwithingroup
Óchangeofvaluestestedby
t-testfortwo-pairedsamples.
EDV
end-diastolicvolume;ESV
end-systolicvolume;LVEF
leftventricularejectionfraction;m
myocardium;S
peaksystolicvelocityofbasalmyocardiumadjacenttomitralannulus;
Sinfarctpeaksystolicvelocityoftheinfarctedwall;
Mean6-siteS
(SlateralSseptalSanteriorSinferiorSanteroseptalSposterior)/6;s
segments;SPECT
singlephoton
emissioncomputedtomography;otherabbreviationsasinTableI.
DiscussionPotentialEffectofCellTherapy
Bonemarrowcontainsagreatnumberof
primitivecellsthatareabletodifferentiate

intospecializedcells,forexampleintoendothe-
lialcellsormyocytes.
20Ð24Someoftheseprim-
itivecellsproducedifferentgrowthfactors,
21forexamplevascularendothelialgrowthfac-

tor,basic
Þbroblastgrowthfactor,andcytokines

withproangiogeneticeffect.Forthesereasons,

manyexperimentalstudieswereperformedand

---

provedthepossibilityofcelltherapytoimprove
perfusionor/andfunctionofdysfunctionalmy-

ocardium.20Ð26Despitenumerousunresolvedquestionscon-
cerningthecelltransplantation,these
Þrsthopefulexperimentalstudieswereimmediately

followedbyclinicaltrials,mostlyinpatients

withacutemyocardialinfarction.Thenum-

bersofpatientsincludedarerelativelysmall.

Manyofthesestudiesarenotrandomized.The

typeandamountofcellsthatarenecessary

toimplanttoreallyregeneratedamagedmy-

ocardiumarenotknown.
Atpresent,wedonotknowthemechanism
ofactionoftheimplantedcellsinstudiesthat

foundimprovementinmyocardialfunctionor

perfusionfollowingthecelltherapy.Recently,

severalexperimentalprojectsdescribednoor

onlynegligibletransdifferentiationofadult

stemcellsintothemyocytes.
27Ð30Thebene
Þtofcelltransplantationmaybeinducedbythe

paracrinestemcelleffect.
3132StudiesinPatientswithAcuteMyocardial
InfarctionsTransplantationofmononuclearbonemar-
rowcellsintotheregionofinfarctedmy-

ocardiumhasbeenpreviouslysuggestedasa

promisingalternativetreatmentforleftven-

tricledysfunction.Nevertheless,theresults

ofrandomizedstudiesarecontroversial.
347Ð9Someofthemindicatedthatpatientswith
themostdepressedleftventricularcontrac-

tilefunctionhadthegreatestimprovementin

contractilefunctionafterintracoronaryadmin-

istrationofbonemarrowcells.Forexample,

REPAIR-AMI,
33sofarthelargestrandomized
multicenterÒcellstudy,
Óshowedsigni
Þcantlygreaterincreaseintheglobalefttejectionfrac-

tioninthebonemarrowcellgroup(5.5%vs.

3.0%inthecontrolgroup)at4monthsfollow-

up.Higherimpactofcellswasfoundamongpa-

tientswithabaselineleftventricleejectionfrac-

tionbelowthemedianvalue(48.9%).Inthese

patients,theabsoluteincreaseinejectionfrac-

tionwasthreetimeshigherthatintheplacebo

group(7.5%ascomparedwith2.5%;absolute

difference:5.0%).Amongpatientswithabase-

lineejectionfractionabovemedian,theabso-

lutedifferencebetweengroupswasonly0.3%

(4.0%vs.3.7%).Similarobservationswerepre-

viouslydescribedinTOPCARE-AMItrial,
34inwhichbaselineleftventricleejectionfraction

wastheonlysigni
Þcantpredictorofimprove-
mentinejectionfractionduringthe4-months
follow-up.
Intherandomized,double-blind,placebo-
controlledstudyofJanssensgroup,
35in67pa-
tientswithST-elevationmyocardialinfarction

treatedwithcoronaryintervention,noeffect

ofautologousbonemarrow-derivedstemcell

transferonleftventricleejectionfractionwas

found.However,thetreatmentwasassociated

withasigni
Þcantreductioninmyocardialin-

farctsizeandbetterrecoveryofregionalsys-

tolicfunction.Theeffectoftreatmentonthe

probabilityofimprovementinregionalfunction

showedapredominantinteractioninthemost

severelyaffectedsegments.Inadditiontothat,

onpositronemissiontomographyexamination,

patientswithlargermyocardialinfarctionhad

agreaterincreaseinmetabolicactivityaftercell

therapythanafterplaceboinfusion.
Ontheotherhand,BOOSTtrial
3637didnot
describetheinverserelationbetweenbaseline

leftventricularejectionfractionandabsolute

improvementoftheleftventriclefunctionaf-

terimplantationofthebonemarrowcellsinto

theinfarctedmyocardium.At6-monthfollow-

up,patientsinacontrolgroupofthisstudyim-

provedtheirejectionfractionfrom51.3%to52%

(0.7%absolutechange),whilethebonemarrow

cellgroupfrom50.0%to56.7%(6.7%absolute

change).Thebonemarrowcellsubgrouppa-

tientswithejectionfractionoftheleftventri-

cle
52%increasedtheirejectionby8.0%,but
patientswithejectionfraction
52%onlyby
4.5%.Themainlimitationofthesestudiesisthe
fact,thatpatientswithonlymildleftventricu-

lardysfunctionwereincluded.
StudiesinPatientswithModerate-to-Severe
LeftVentricularDysfunction
Thereareonlyfewtrialsstudyingcellther-
apyinpatientswithmoderate-to-severeleft

ventriculardysfunctionandtheirresultsare

controversialtoo.Bartuneketal.
3describedimprovementoftheleftventricularperfor-

manceandincreasedmyocardialperfusionand

viabilityamongpatientswithacutemyocar-

dialinfarctiontreatedwithstentingandintra-

coronaryadministrationofCD133
progenitorcells.Theleftventricularejectionfractionin-

creasedfrom45.0%to52.1%.
Controversially,ASTAMItrial
11didnot
Þndanysigni
Þcantdifferencebetween47patients
treatedwithcelltransplantationsand50pa-

tientsinthecontrolgroup.Theleftventricular

ejectionfractionandend-diastolicvolumewere
assessedbysinglephotonemissioncomputed

tomography,echocardiography,andmagnetic

resonance.Improvementversusbaselineval-

ueswasfoundinbothgroups,buttheydidnot

signiÞcantlydiffer.Resultswereconsistentfor
allthethreemethods.Noimprovementincar-

diacfunctionwasalsofoundinKuetheetal.
38intheirstudywith
Þvepatientswithalargeacute
anteriormyocardialinfarctionandintracoro-

narymononuclearbonemarrowcellimplanta-

tion.Inourpreviousstudy,
12thesigni
Þcantand
dose-relatedimprovementwasfoundinthere-

gionalsystolicfunctionoftheinfarctedwallaf-

tercelltransplantation.Ascomparedtocon-

trols,ahighercelldosesigni
Þcantlyimproved
globalLVsystolicfunction.Bothcelldosespre-

ventedtheleftventriclefromthedilation,while

theend-diastolicvolumesigni

Þcantlyincreased
inthecontrolgroup.Becausepatientswiththe

greatestdamagetotheirmyocardiumarethe

oneswhoneedtreatmentmost,thesubstudy

ofthesepatientswasperformed.Inthissub-

studythestatisticallyimportanteffectofau-

tologoustransplantationofmononuclearbone

marrowcellsonmyocardialfunctionwasnot

foundinpatientswithmoderate-to-severeleft

ventriculardysfunction.Onlyaninsigni
Þcanttrendtowardthepreventionoftheleftventric-

ulardilatationandimprovementofgloballeft

ventricleejectionfractionwasfoundat3-month

follow-up.
StudyLimitations
Exceptthefactthatourstudyissubanalysis,
themajorlimitationsofourstudyarethesmall

numberofpatientsenrolled.However,tothis

momentitisoneofthestudieswiththehighest

numberofpatientswithmoreseverereleftven-

triculardysfunctioneverpublished.Compared

tootherstudies,theveryrigorousmyocardial

viabilityassessmentwasperformedbeforein-

clusiontothisstudy.
Thegroupsdifferslightlyintimefromon-
setofinfarctiontoreperfusion.Thedifferences

werenotstatisticallysigni
Þcant.Thehetero-
geneitywascausedbytheinclusionoftwopa-

tientswithdelayedcoronaryangioplasty(one

patientintheGroupHandonepatientinthe

GroupC).Inourpreviousstudythebiggest

effectofcelltransplantationswasfoundbe-

tweenhigherdoseandcontrolgroups.Inthis

study,thedifferenceintimefrominfarcton-

settoreperfusionbetweenGroupsHandCwas
just23minutes.Sothisdifferencehasnotbeen
supposedtoaffecttheresults.
Becauseofethicalconsideration,thepatients
includedintothecontrolgroupdidnotundergo

theidenticalprocedures,asdidthebonemar-

rowcellpatients,beingexcludedfromthebone

marrowaspirationandcoronaryangiography

withtheshamcelltransplantation.Fortechni-

calreasons,thepositronemissiontomography

(PET)wasnotperformedinallourpatients.
Inadditiontothelimitedstudypopulation,
anotherexplanationofourresultscouldbethe

veryseveremyocardialdamagewithalmostno

survivingmyocytes.Intheseconditions,thereis

nosuitablemilieuforcatchingimplantedcells

andtheirdifferentiationintocardiomyocytes.

Alsotheseveredestructionofmicrocirculation

couldmakethecellhomingmoredif
Þcultcom-
paredtopatientswithlessseveremyocardial

damage.
ConclusionTheimportantthingisthefactthattheselec-
tionofcellsandthewholemethodofcellther-

apyarejustatthebeginningoftheway.Prob-

ably,itisnotrealistictoexpectsomegreater

changesofleftventriclefunctioninthismanner

oftreatment.Itisnecessarytolookforthebest

celltype,anoptimalwayandtimeofcelldeliv-

ery,andthehelpofsomecytokines.Forsolving

theseclinicalquestions,wemustalsobetterun-

derstandthemechanismsofpotentialpositive

effectofthecelltherapy.

Takingtogether,theresultsoftrialsshow
thatthereisstillworktobedonetounderstand

alotofquestionsrelatedtothecelltherapy.Fur-

therstudies,includinglargernumbersofpa-

tients,areneededtoresolveallthesetasks.
References1.HoKK,AndersonKM,KannelWB,etal:Survivalaf-
tertheonsetofcongestiveheartfailureinFraming-

hamHeartStudysubjects.
Circulation1993;88:107Ð115.2.RosamondW,FlegalK,FridayG,etal:Heartdis-
easeandstrokestatistics
Ð2007update.Areportfrom
theAmericanHeartAssociationStatisticsCommit-

teeandStrokeStatisticsSubcommittee.
Circulation2007;115:e69Ðe171.3.BartunekJ,VanderheydenM,VandekerckhoveB,
etal:IntracoronaryinjectionofCD133-positiveen-

richedbonemarrowprogenitorcellspromotescardiac

recoveryafterrecentmyocardialinfarction:Feasibil-

ityandsafety.
Circulation2005;112(Suppl.):I-178ÐI-183.4.Fern
«andez-Avil
«esF,SanRom
«anJA,Garc
«õa-Frade
J,etal:Experimentalandclinicalregenerative

---

capabilityofhumanbonemarrowcellaftermyocar-
dialinfarction.
CircRes
2004;95:742Ð748.5.FuchsS,SatlerLF,KornowskiR,etal:Catheter-
basedautologousbonemarrowmyocardialinjec-

tioninno-optionpatientswithadvancedcoronary

arterydisease.Afeasibilitystudy.
JAmCollCardiol
2003;41(10):1721Ð1724.6.Gali
÷nanesM,LoubaniM,DaviesJ,etal:Auto-
transplantationofunmanipulatedbonemarrowinto

scarredmyocardiumissafeandenhancescar-

diacfunctioninhumans.
CellTransplant
2004;13:7Ð13.7.HamanoK,NishidaM,HirataK,etal:Localimplan-
tationofautologousbonemarrowcellsfortherapeu-

ticangiogenesisinpatientswithischemicheartdis-

ease.Clinicaltrialandpreliminaryresults.
JpnCirc
J2001;65:845Ð847.8.ChenSL,FangWW,YeF,etal:Effectonleftven-
tricularfunctionofintracoronarytransplantationof

autologousbonemarrowmesenchymalstemcellinpa-

tientswithacutemyocardialinfarction.
AmJCardiol
2004;94:82Ð95.9.StammC,WestphalB,KleineHD,etal:Autologous
bone-marrowstem-celltransplantationformyocar-

dialregeneration.
Lancet2003;361:45Ð46.10.TseHF,KwongYL,ChanJKF,etal:Angiogenesisin
ischaemicmyocardiumbyintramyocardialautologous

bonemarrowmononuclearcellimplantation.
Lancet2003;361:47Ð49.11.LundeK,SolheimS,AakhusS,etal:Intracoronary
injectionofmononuclearbonemarrowcellsinacute

myocardialinfarction.
NEnglJMed
2006;355:1199Ð1209.12.MeluzinJ,MayerJ,GrochL,etal:Autologoustrans-
plantationofmononuclearbonemarrowcellsinpa-

tientswithacutemyocardialinfarction:Theeffectof

thedoseoftransplantedcellsonmyocardialfunction.

AmHeartJ
2006;152:975.e9Ð975.e15.13.SchillerNB,ShahPM,CrawfordM,etal:Recom-
mendationsforquantitationoftheleftventricleby

two-dimensionalechocardiography.
JAmSocEchocar-
diogr1989;2:358Ð367.14.Meluz
«õnJ,CigarroaCG,BricknerE,etal:Dobu-
tamineechocardiographyinpredictingimprovement

ingloballeftventricularsystolicfunctionaftercoro-

narybypassorangioplastyinpatientswithhealed

myocardialinfarcts.
AmJCardiol
1995;76:877Ð880.15.WandtB,FornanderY,EgerlidR:Maximallongitu-
dinalcontractionvelocityinassessmentofleftven-

tricularsystolicfunction:ApulsedtissueDopplerand

M-modestudy.
Echocardiography
2004;21(7):587Ð592.16.YudaS,InabaY,FujiiS,etal:Assessmentofleft
ventricularejectionfractionusinglong-axissystolic

functionisindependentofimagequality:Astudy

oftissueDopplerimagingandM-modeechocar-

diography.
Echocardiography
2006;23(10):846Ð852.17.DakikHA,HowellJF,LawrieGM,etal:Assessment
ofmyocardialviabilitywith99mTc-sestamibitomog-

raphybeforecoronarybypassgraftsurgery.
Circula-
tion1997;96:2892Ð2898.18.MaesAF,BorgersM,FlamengW,etal:Assessmentof
myocardialviabilityinchroniccoronaryarterydisease

usingtechnetium-99msestamibiSPECT.
JAmColl
Cardiol1997;29:62Ð68.19.StrauerBE,BrehmM,ZeusT,etal:Repairof
infarctedmyocardiumbyautologousintracoronary

mononuclearbonemarrowcelltransplantationinhu-

mans.
Circulation2002;106:1913Ð1918.20.TomitaS,LiRK,WeiselRD,etal:Autologoustra
ns-
plantationofbonemarrowcellsimprovesdamaged

heartfunction.
Circulation1999;100(Suppl.II):II-247ÐII-
256.21.FuchsS,BaffourR,ZhouYF,etal:Transendocar-
dialdeliveryofautologousbonemarrowenhancescol-

lateralperfusionandregionalfunctioninpigswith

chronicexperimentalmyocardialischemia.
JAmColl
Cardiol2001;37:1726Ð1732.22.MakinoS,FukudaK,MiyoshiS,etal:Cardiomyocytes
canbegeneratedfrommarrowstromalcellsinvitro.

JClinInvest
1999;103:697Ð705.23.JacksonKA,MajkaSM,WangH,etal:Regenera-
tionofischemiccardiacmuscleandvascularendothe-

liumbyadultstemcells.
JClinInvest
2001;107:1395Ð1402.24.HamanoK,LiTS,KobayashiT,etal:Theinductionof
angiogenesisbytheimplantationofautologousbone

marrowcells:Anovelandsimpletherapeuticmethod.

Surgery2001;130:44Ð54.25.OrlicD,KajsturaJ,ChimentiS,etal:Mobilized
bonemarrowcellsrepairtheinfarctedheart,improv-

ingfunctionandsurvival.
ProcNatlAcadSci(USA
)2001;98:0344Ð0349.26.OrlicD,KajsturaJ,ChimentiS,etal:Bonemar-
rowcellsregenerateinfarctedmyocardium.
Nature2001;410:701Ð705.27.LimbourgFP,Ringes-LichtenbergS,SchaeferA,etal:
Haematopoieticstemcellsimprovecardiacfunction

afterinfarctionwithoutpermanentcardiacengraft-

ment.EurJHeartFailure
2005;7:722Ð729.28.BalsamLB,WagersAJ,ChristensenJL,etal:
Haematopoieticstemcellsadoptmaturehaematopoi-

eticfatesinischaemicmyocardium.
Nature2004;428:668Ð673.29.MurryChE,SoonpaaMH,ReineckeH,etal:
Haematopoieticstemcellsdonottransdifferentiate

intocardiacmyocytesinmyocardialinfarcts.
Nature2004;428:664Ð668.30.NygrenJM,JovingeS,BreitbachM,etal:Bone
marrow-derivedhematopoieticcellsgeneratecar-

diomyocytesatalowfrequencythroughfusion,butnot

transdifferentiation.NatureMedicine
2004;10:494Ð501.31.KinnairdT,StabileE,BurnettMS,etal:Localdeliv-
eryofmarrow-derivedstromalcellsaugmentscollat-

eralperfusionthroughparacrinemechanisms.
Circu-lation2004;109:1543Ð1549.32.MisaoY,TakemuraG,AraiM,etal:Bonemarrow-
derivedmyocyte-likecellsandregulationofrepair-

relatedcytokinesafterbonemarrowcelltransplan-

tation.CardiovascRes
2006;69:476Ð490.33.SchachingerV,ErbsS,ElsasserA,etal:TheREPAIR-
AMIInvestigators.Intracoronarybonemarrow-

derivedprogenitorcellsinacutemyocardialinfarc-

tion.NEnglJMed
2006;355:1210Ð1221.34.Sch
¬achingerV,AssmussB,BrittenMB,etal:Trans-
plantationofprogenitorcellsandregenerationen-

hancementinacutemyocardialinfarction.Finalone-

yearresultsoftheTOPCARE-AMItrial.
JAmColl
Cardiol2004;44:1690Ð1699.35.JanssensS,DuboisC,BogaertJ,etal:Autol-
ogousbonemarrow-derivedstem-celltransferin

----------CELLTHERAPYINANACUTEMYOCARDIALINFARCTION
patientswithST-segmentelevationmyocardialinfarc-
tion:Double-blind,randomisedcontrolledtrial.2006;

367(9505):113Ð121.36.WollertKC,MeyerGP,LotzJ,etal:Intracoronaryau-
tologousbone-marrowcelltransferaftermyocardial

infarction:TheBOOSTrandomizedcontrolledclinical

trial.Lancet2004;363:141Ð148.37.MeyerGP,WollertKC,LotzJ,etal:Intracoronar
y

bonemarrowcelltransferaftermyocardialinfarction.
Eighteenmonths
Õfollow-updatafromtherandomized,
controlledBOOST(bonemarrowtransfertoenhance

ST-elevationinfarctregeneration)Trial.
Circulation2006;113:1287Ð1294.38.KuetheF,RichartzBM,SayerHG,etal:Lackofre
gen-
erationofmyocardiumbyautologousintracoronary

mononuclearbonemarrowcelltransplantationinhu-

manswithlargeanteriormyocardialinfarctions.
IntJCardiol
2004;97:123Ð127.Vol.25,No.8,2008
ECHOCARDIOGRAPHY:AJrnl.ofCVUltrasound&AlliedTech.
897