TURIN, 20TH—21ST NOVEMBER 2008

GREAT INNOVATIONS IN CARDIOLOGY

4TH JOINT MEETING WITH MAYO CLINIC

4TH TURIN CARDIOVASCULAR NURSING CONVENTION

SESSION II:
PERSPECTIVES IN ISCHEMIC HEART DISEASE (PART II)

N. Caplice (Cork—Ireland)

Cell therapy for acute Myocardial Infarction:
where are we at in 2008?

Cell Therapy for Acute MI-2008

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Torino Nov 2008

Porcine AMI model for Cell Therapy

- 90 min balloon occlusion in pig LCx /LAD coronary artery
- Autologous cell therapy (CPC or MNC) at 48 hours post AMI
- PET-CT tracking of CPC post therapy
- Cardiac MRI imaging(+/- Gd) at 48 hours and 2 months post AMI

Model TOPCARE AMI Clinical Trial

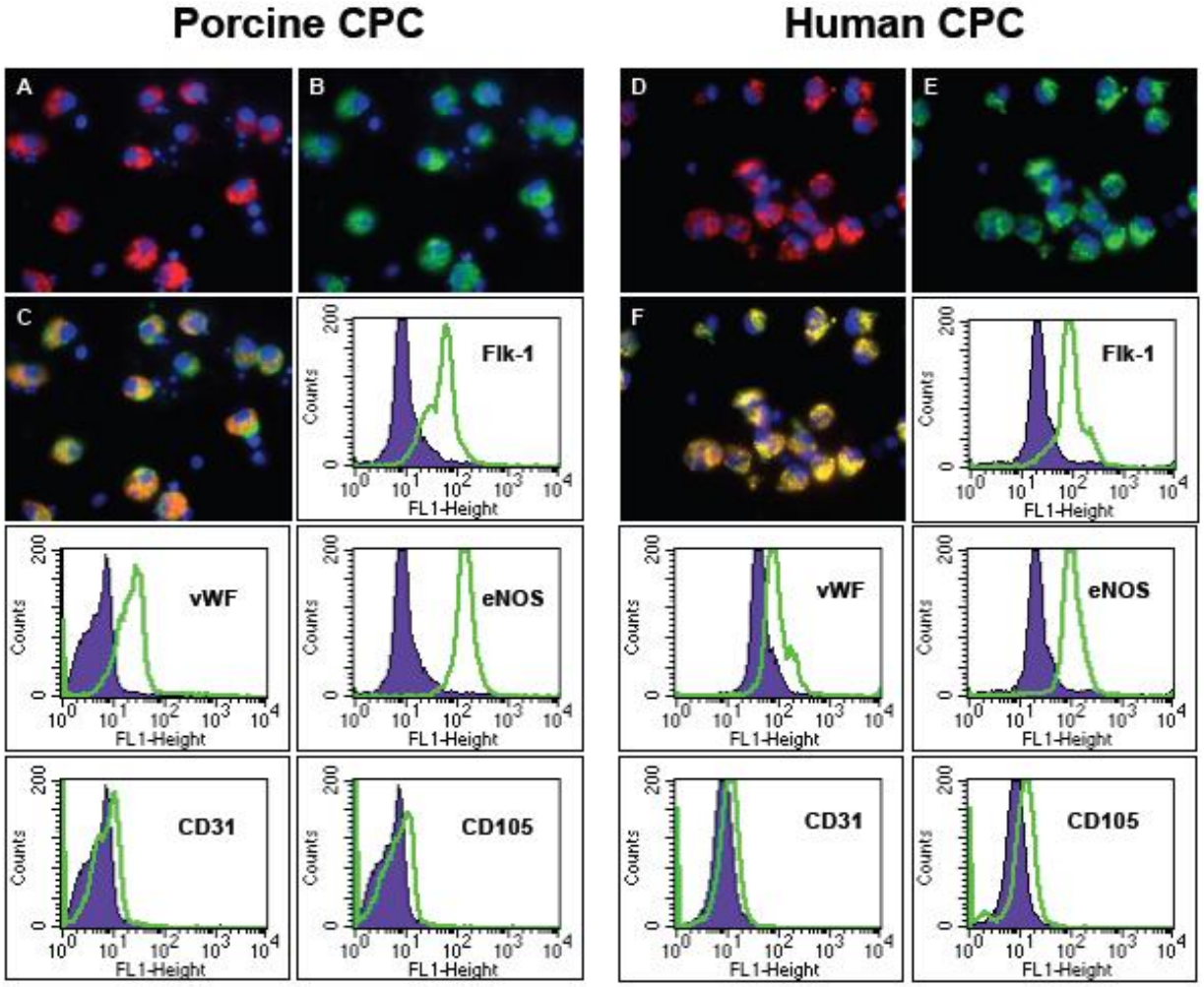
Experimental AMI model

Tracking of CPC *in vivo*

&

Determining Paracrine Effects

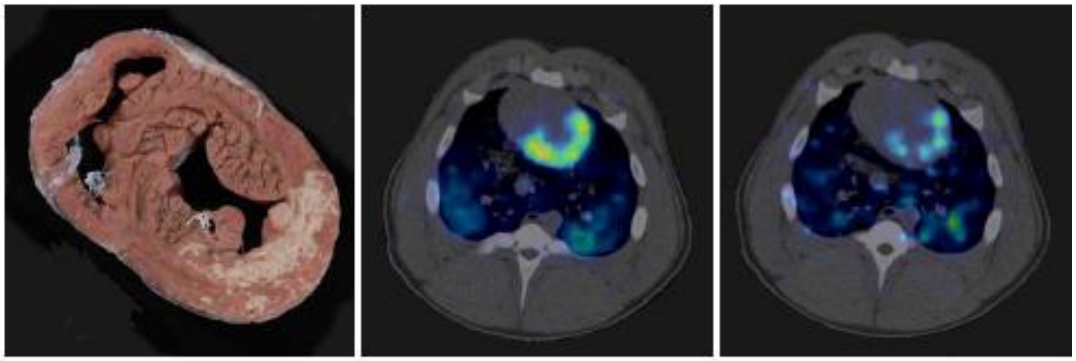
Human and porcine circulating progenitor cells (CPC)



CPC cultured on FN and EPC medium

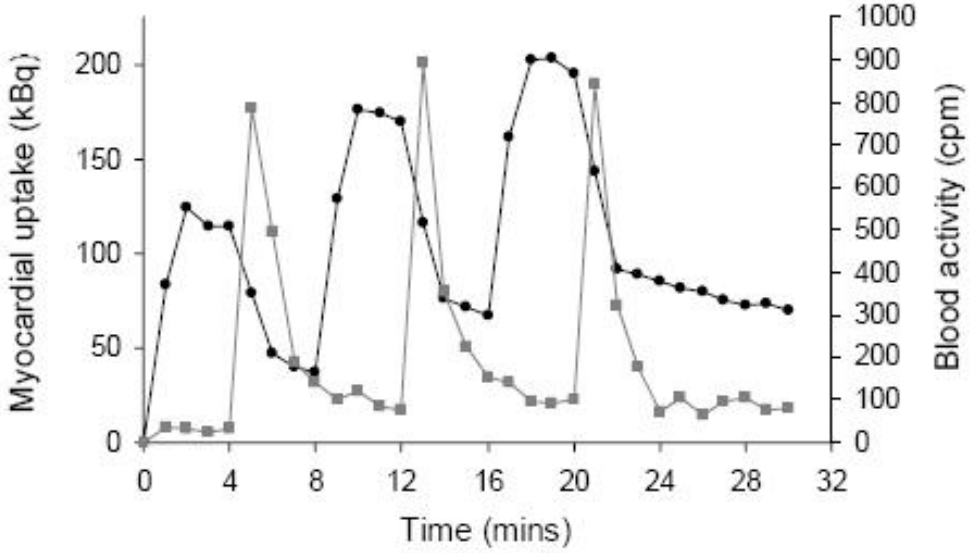
Dynamic tracking of ^{18}F-FDG labeled CPC during intracoronary injection in porcine AMI

A



Myocardial infarction Post-injection 1 hour

B

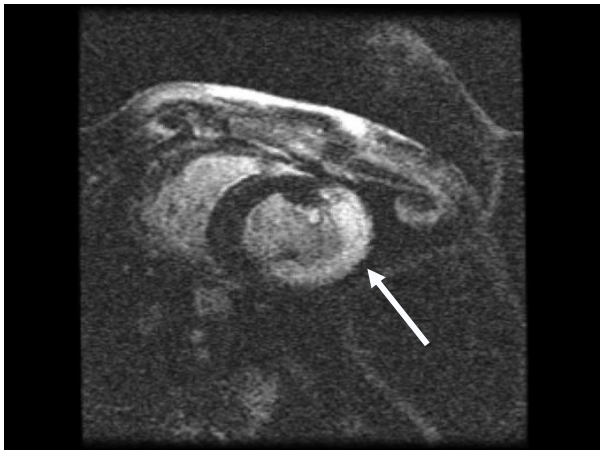


Group 1: Intermittent balloon occlusion

Doyle et al
J Nucl Med 2007

Myocardial Infarct size -MRI

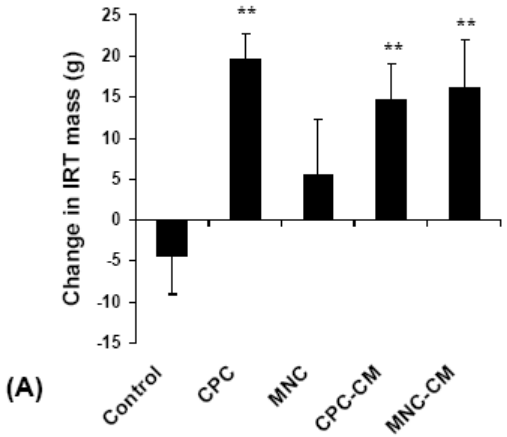
	CTL	CPC	MNC
Infarct size-LCx (g)	12.5 ±1.2	6.0 ±1.9	13.4 ±3.0
Infarct size (% of LV mass)	16.6 ±1.7	8.7 ±2.7	17.6 ±3.2

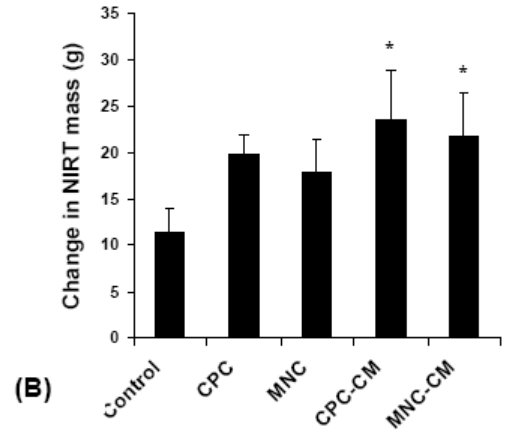


Transmural MI Gd HE

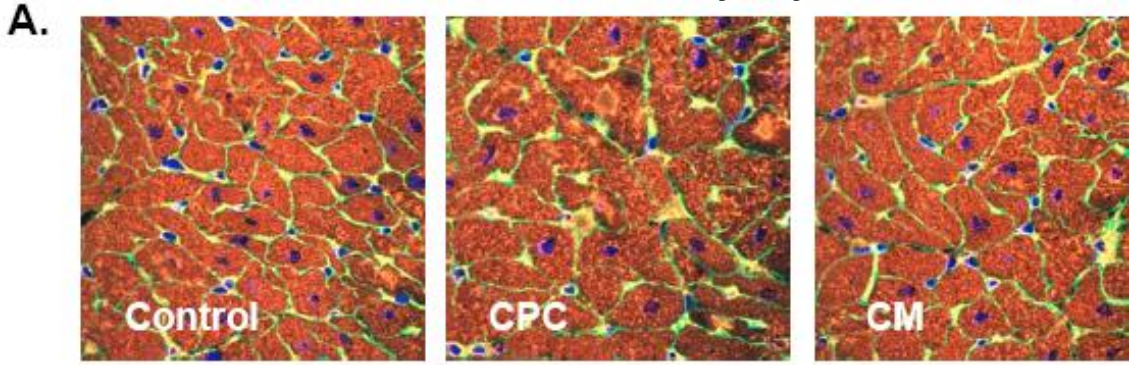
24 animals studied

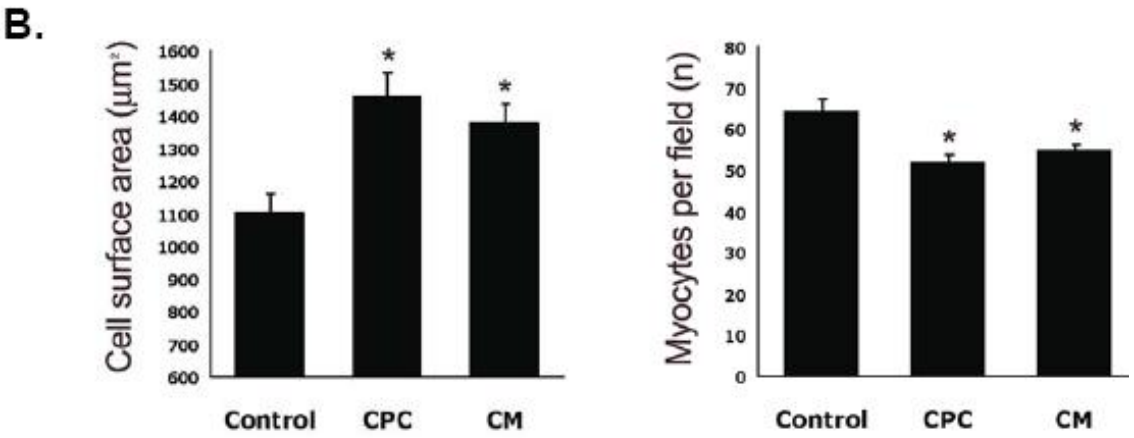
Paracrine factors from CPC induce border zone (IRT) hypertrophy post AMI





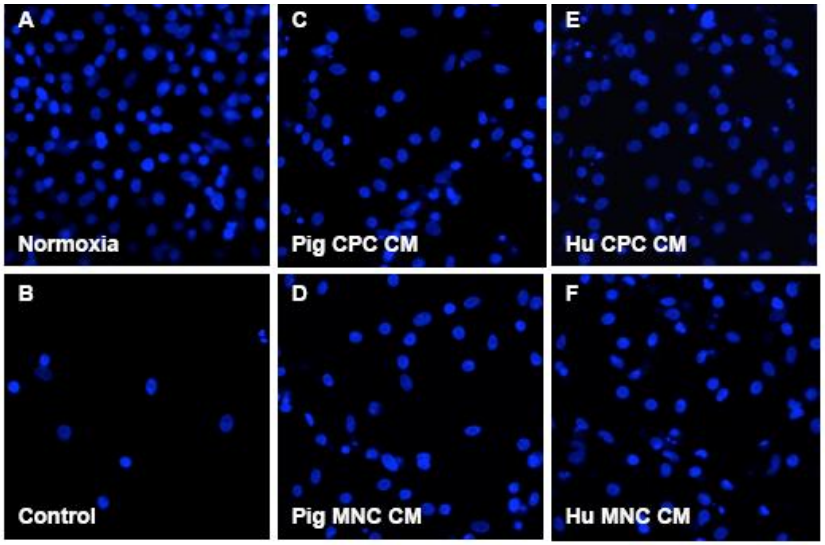
Border zone cardiomyocytes

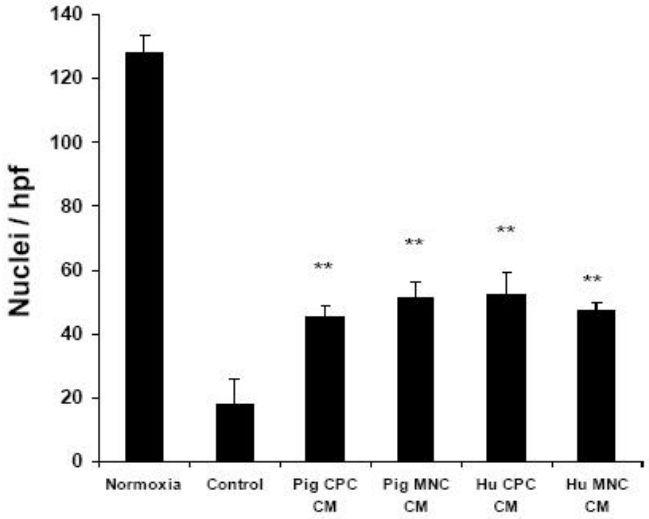




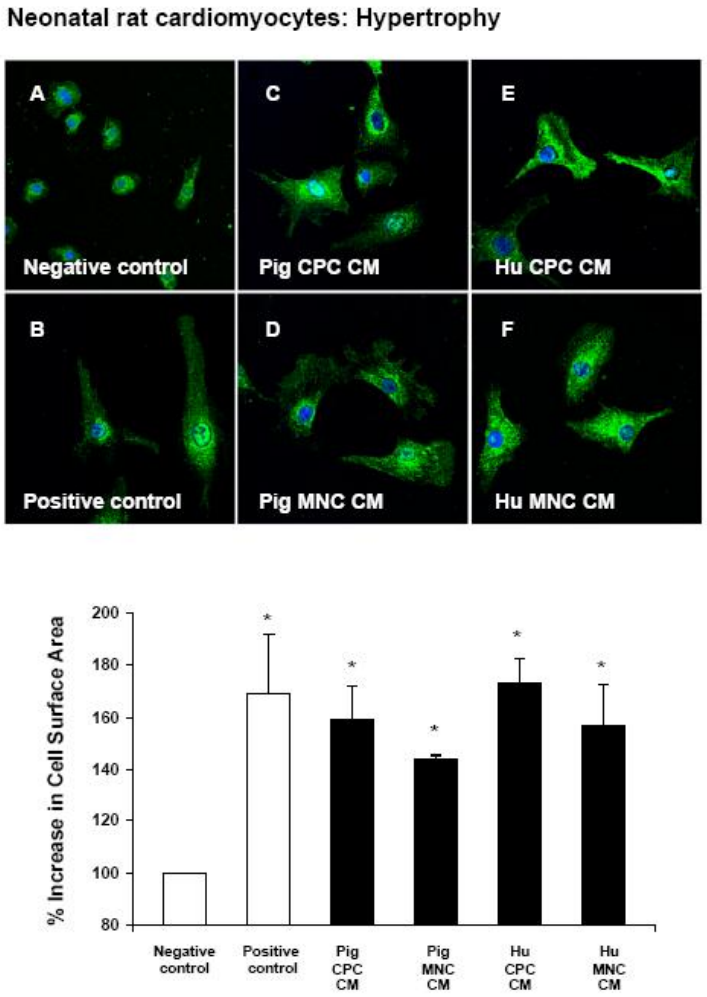
Doyle et al Stem Cells Dev 2008

Secreted factor(s) from CPC/MNC augment cardiomyocyte survival post hypoxia





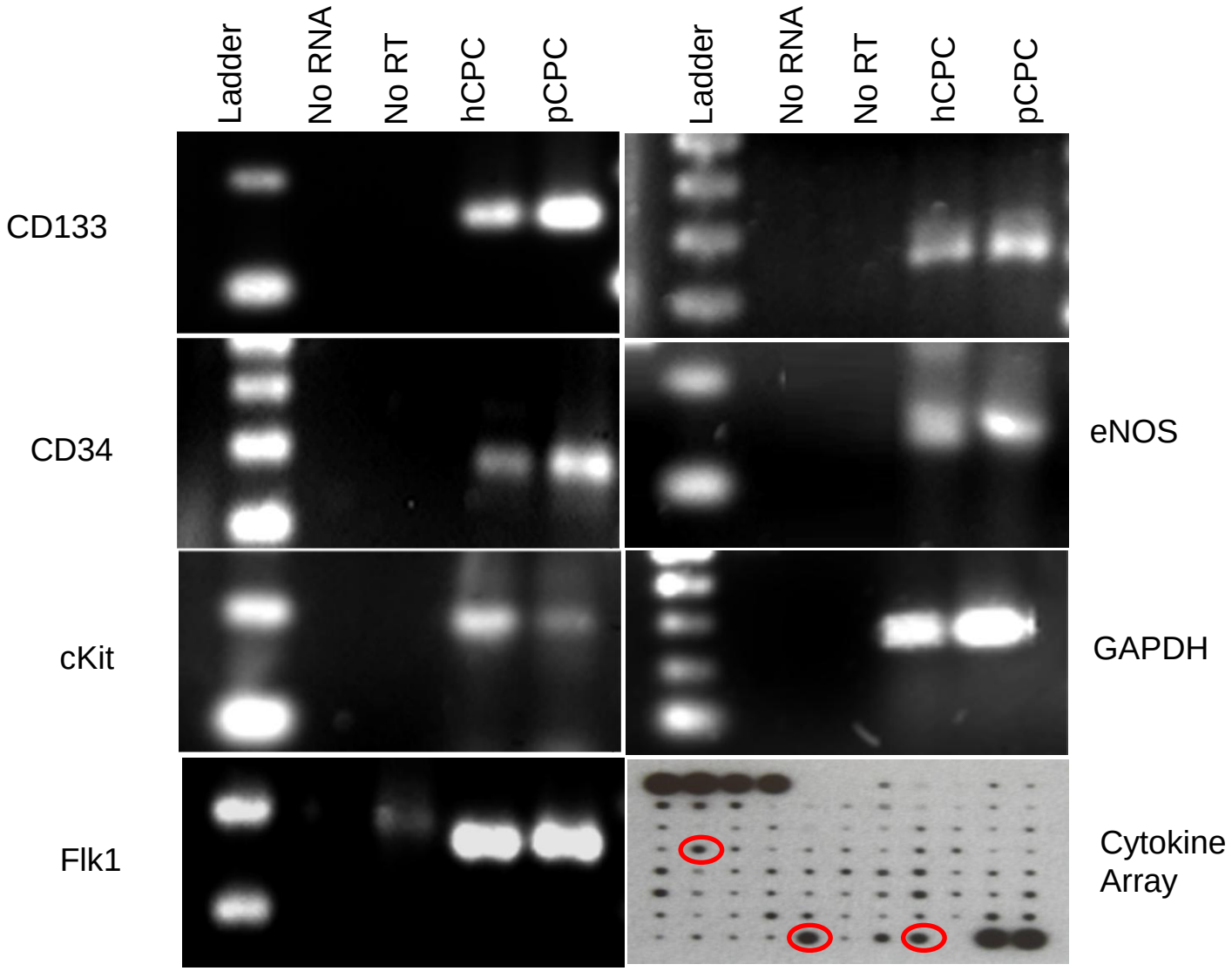
Secreted factor(s) from CPC/MNC augment cardiomyocyte hypertrophy *in vitro*



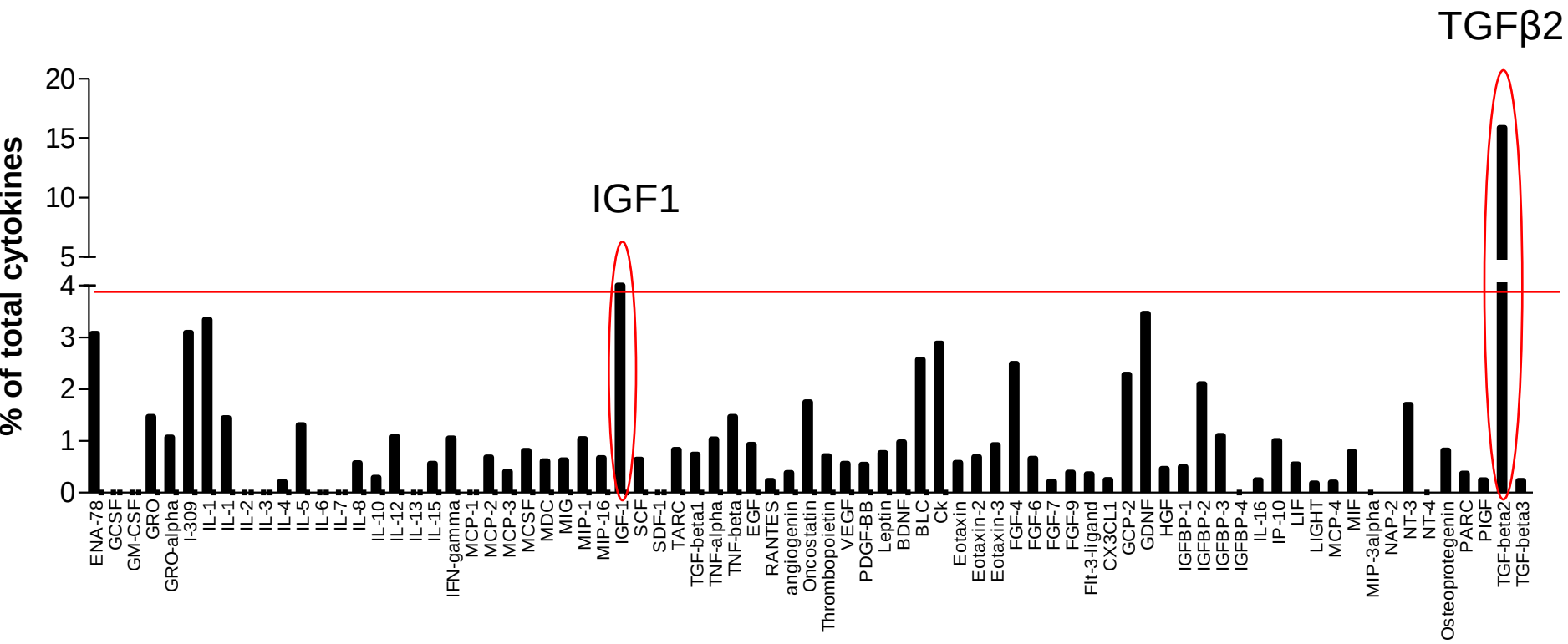
Progenitor-derived Paracrine Factors

- In vitro effects on hypoxic cardiomyocytes
- Acute repair and pro-survival effects
- Acute in vivo hemodynamic effects
- Chronic in vivo hemodynamic
- Chronic cardiotrophic effects

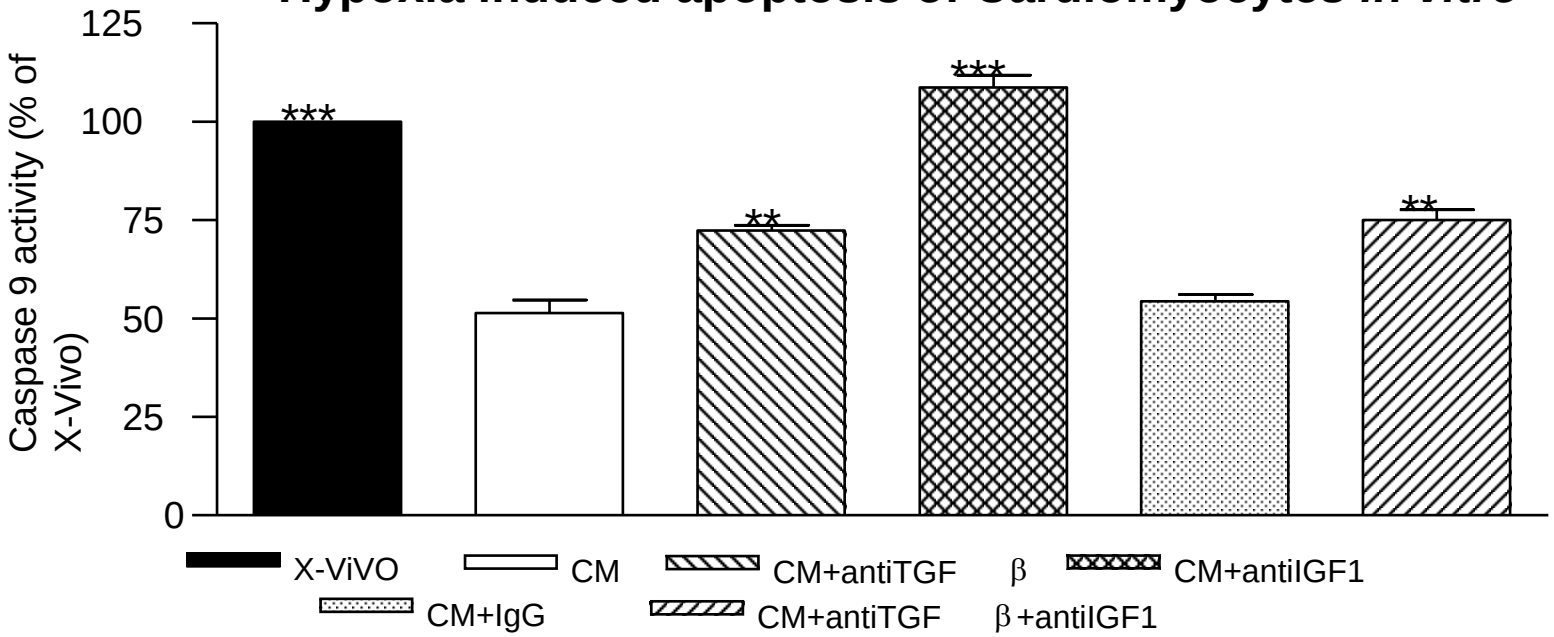
Porcine endothelial progenitor cells transcriptional signature

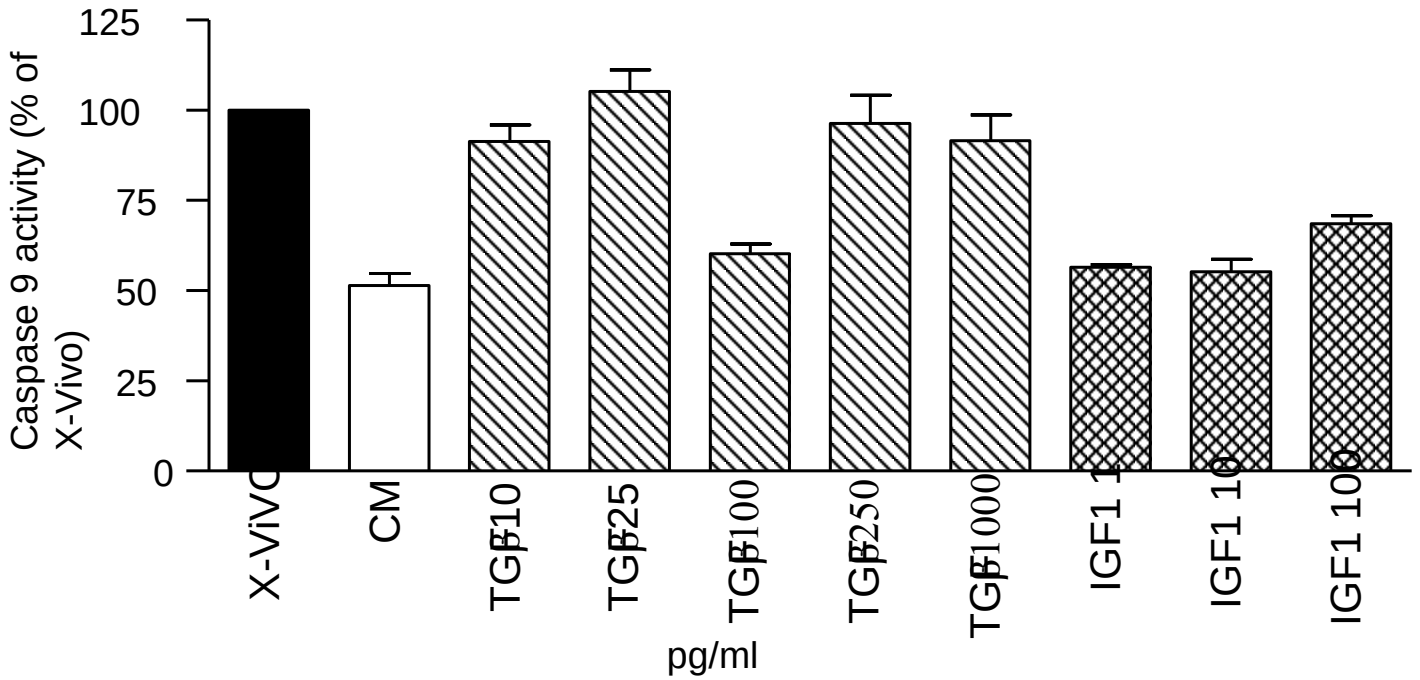


Cytokines secreted from porcine EPC *in vitro*

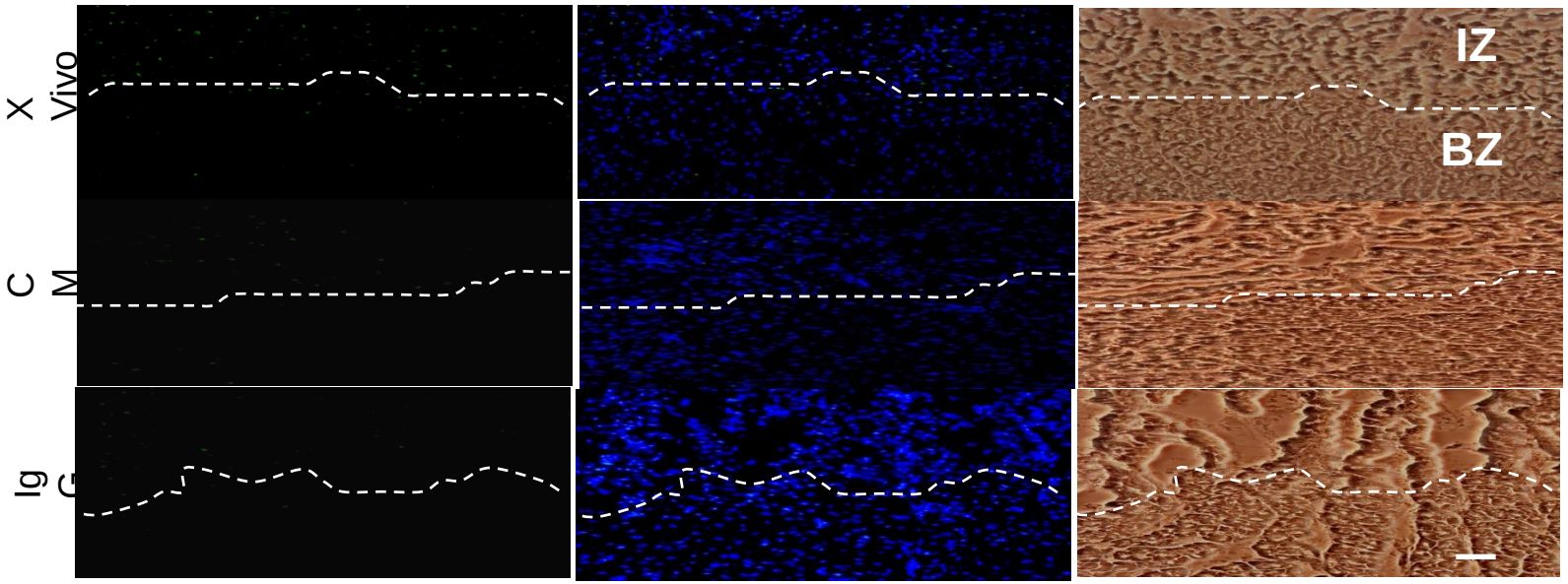


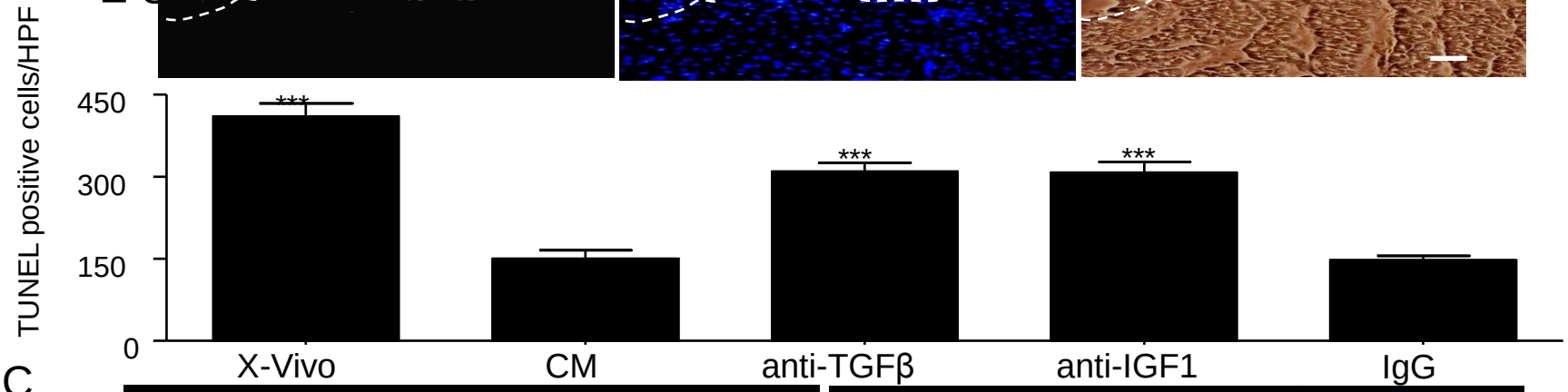
Hypoxia induced apoptosis of Cardiomyocytes *in vitro*



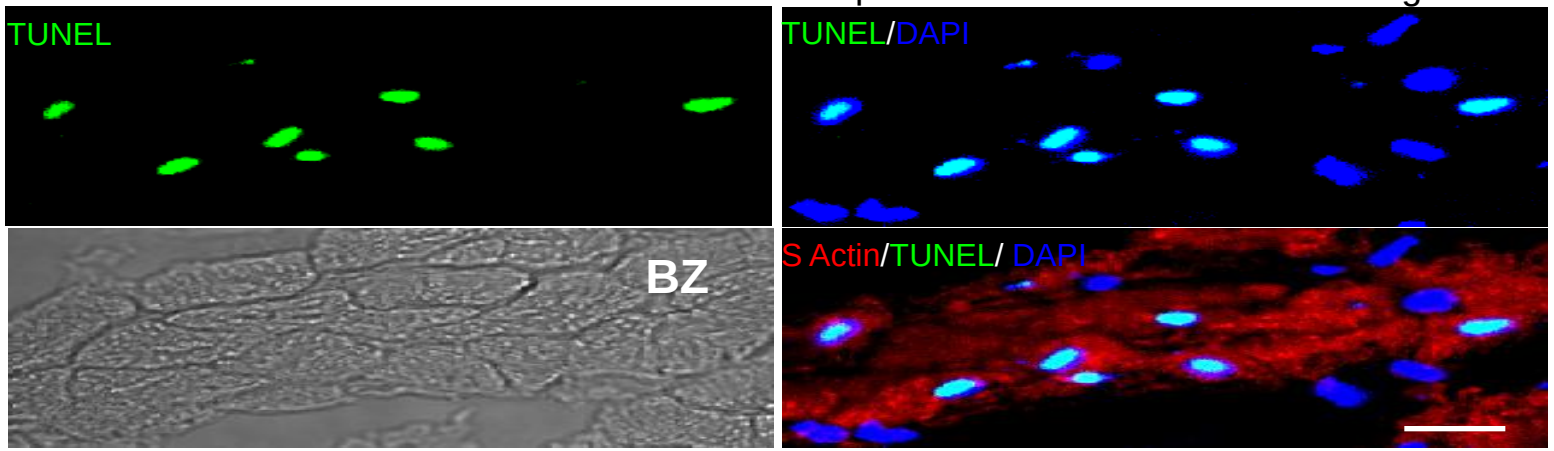


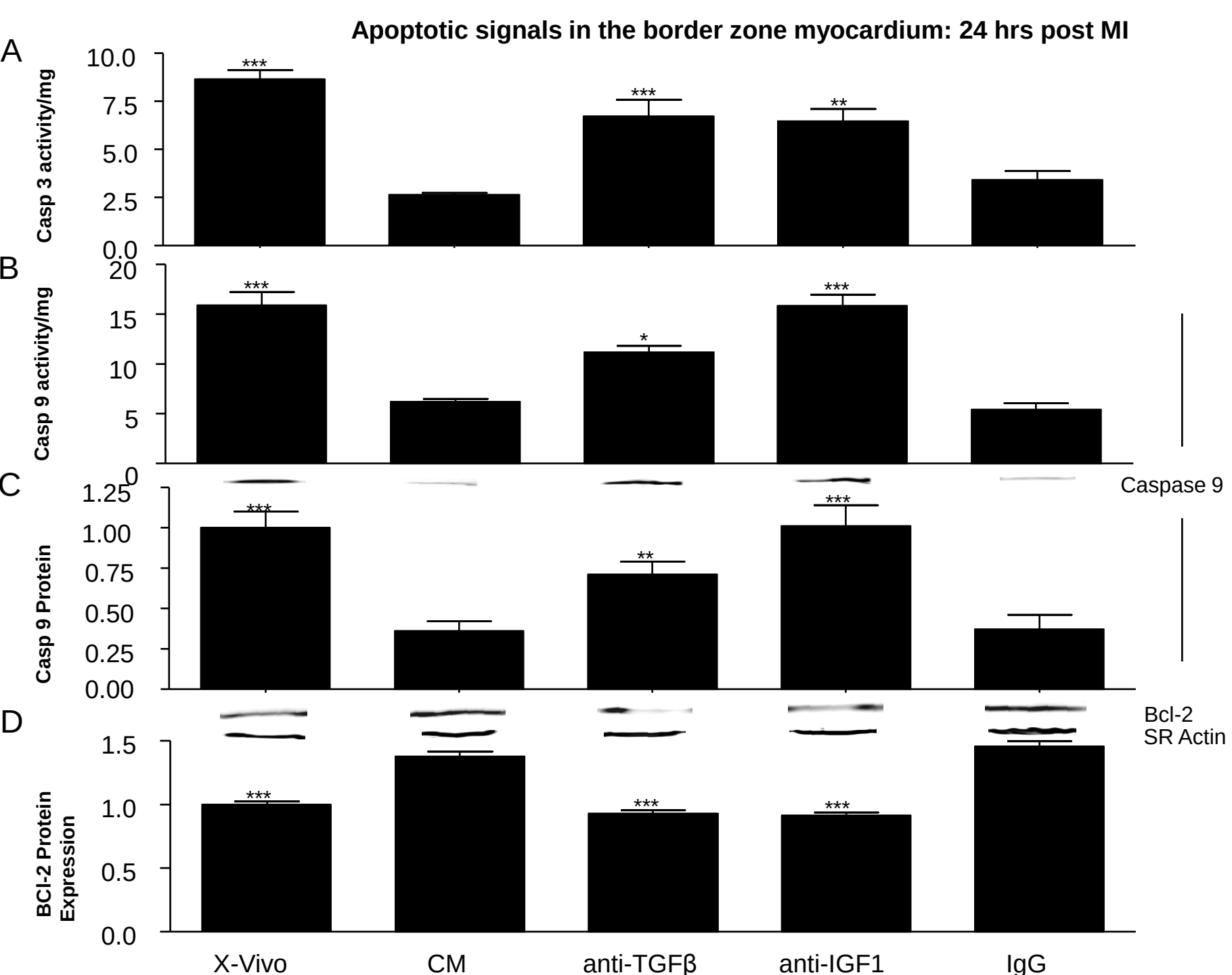
Inhibiting GFs in CM abrogates anti-apoptosis effect in border zone of post AMI



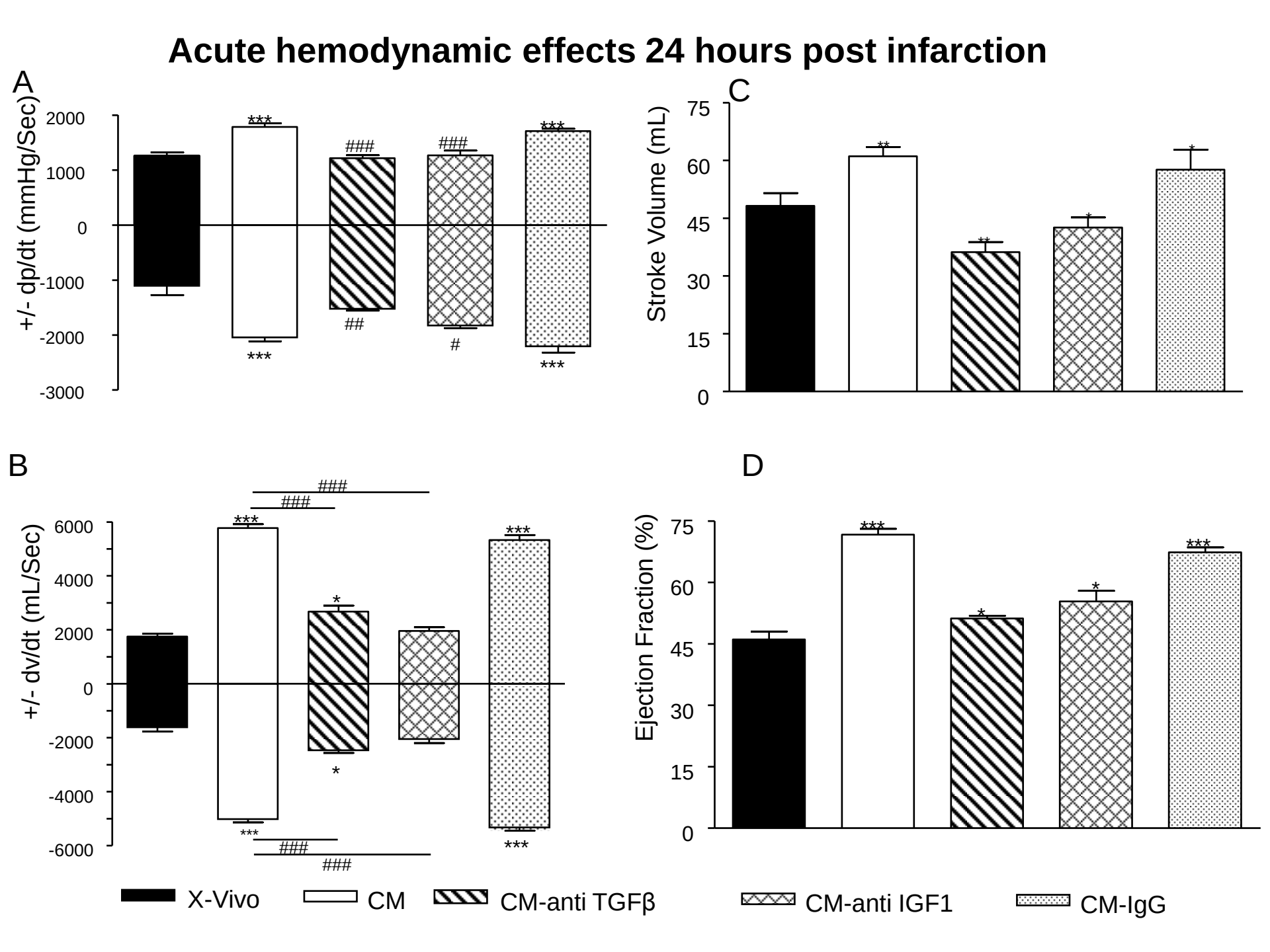


C

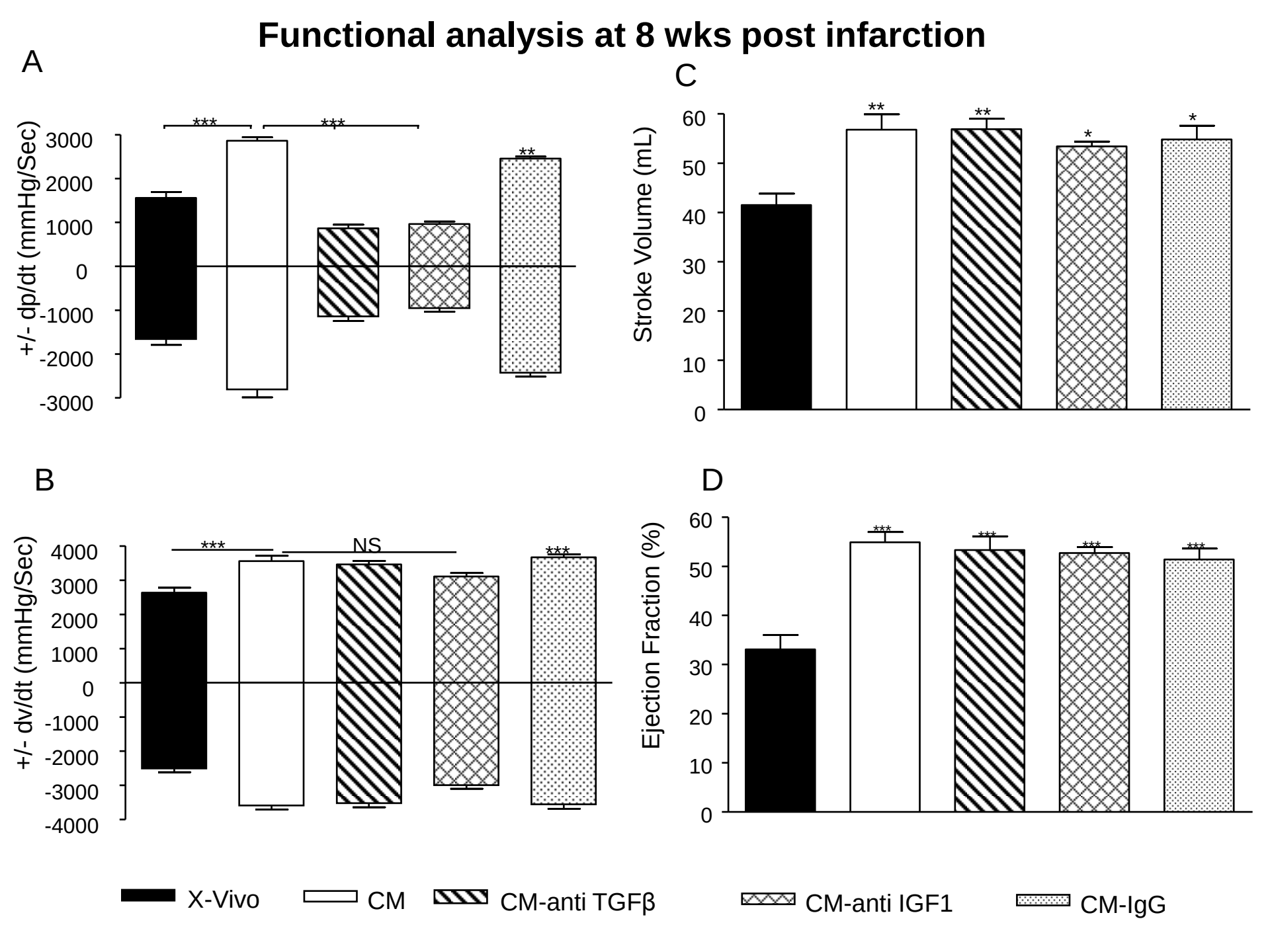



Apoptotic signals in the border zone myocardium: 24 hrs post MI
A
Casp 3 activity/mg
10.0
7.5
5.0
2.5
0.0
***
***
**
B
Casp 9 activity/mg
20
15
10
5
0
***
*
***
Caspase 9
C
Casp 9 Protein
1.25
1.00
0.75
0.50
0.25
0.00
***
**
***
D
BCl-2 Protein Expression
1.5
1.0
0.5
0.0
***
***
***
Bcl-2
SR Actin
X-Vivo
CM
anti-TGFβ
anti-IGF1
IgG

Acute hemodynamic effects 24 hours post infarction



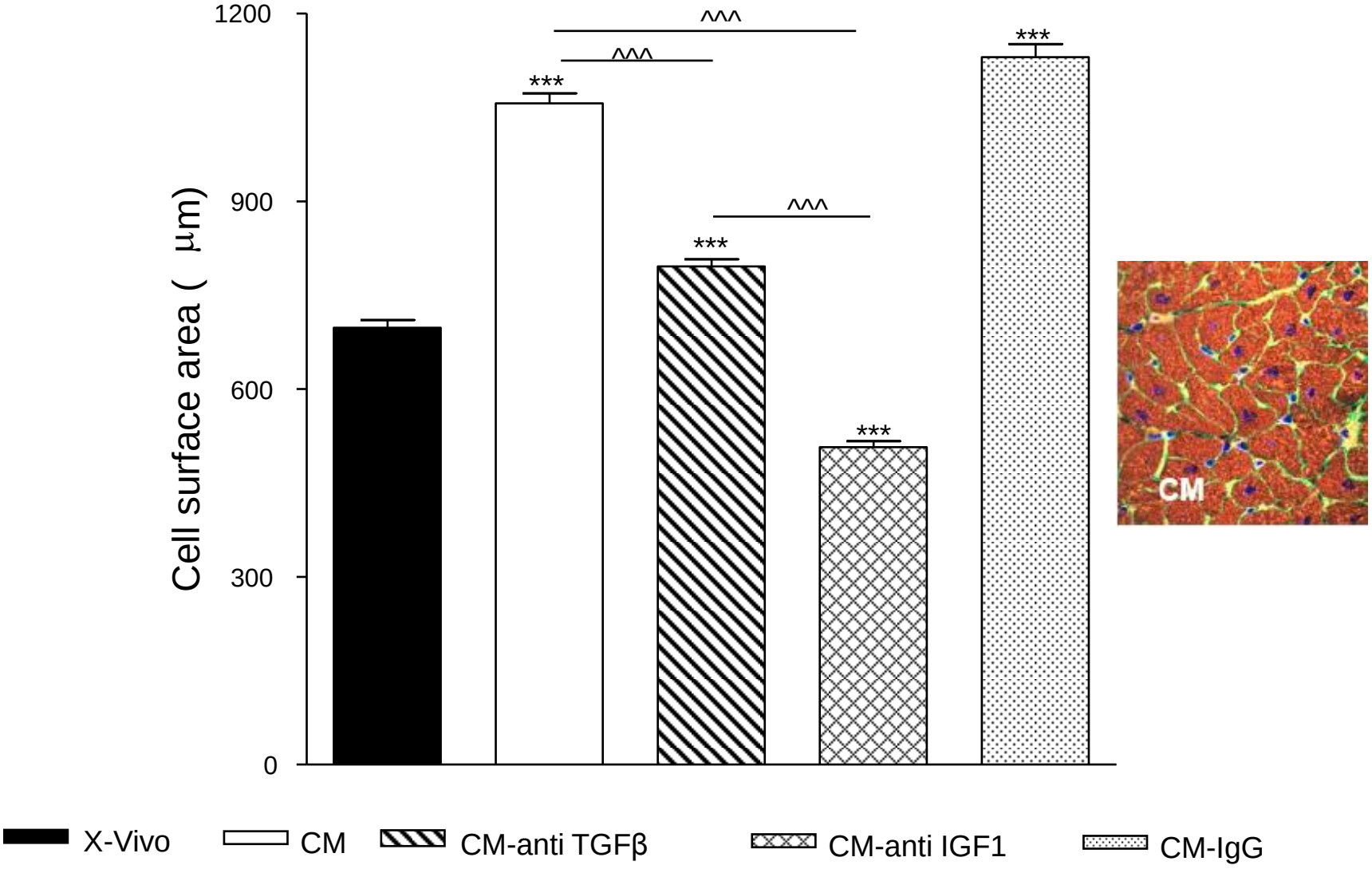
Functional analysis at 8 wks post infarction

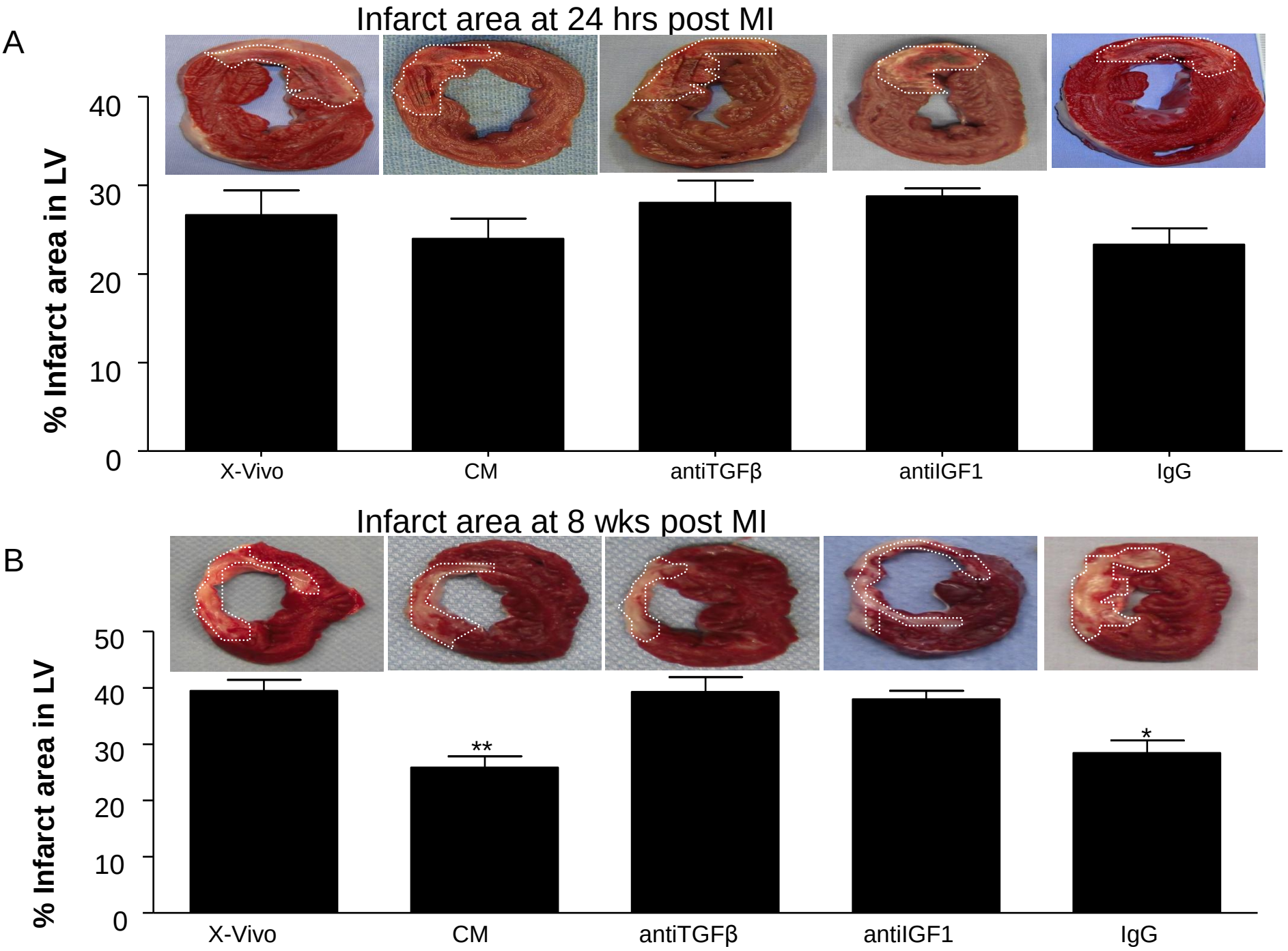


LV Remodeling at 8 weeks post infarction

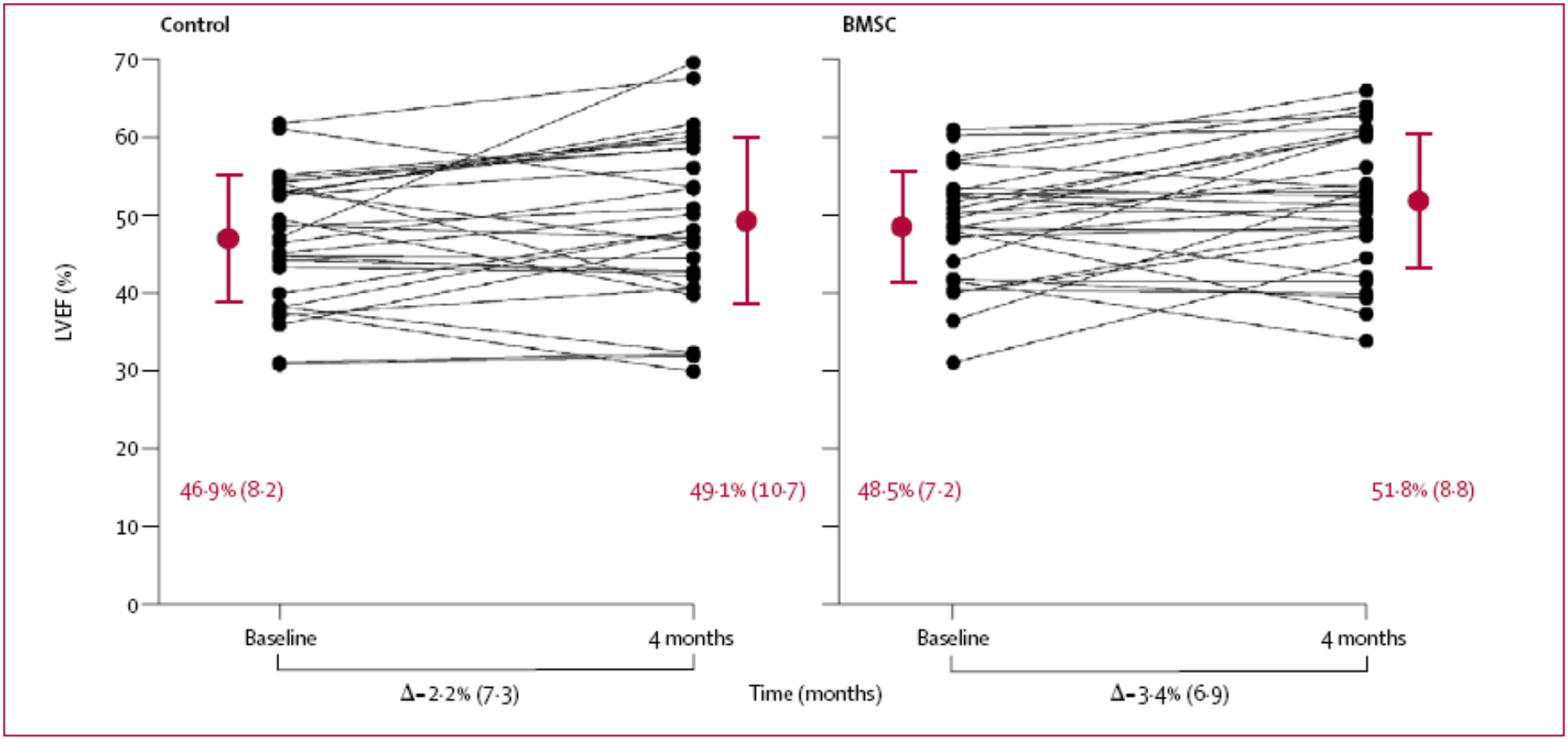
	X-vivo	CM	IGF1ab	TGFβ ab	IgG
ESV (mL)	**79.4±4.3**	**37.4±1.9 ***	**32.2±1.1**	**31.2±2.2**	**38.1±1.3**
EDV (mL)	**130.4±8.6**	**98.2±11.1 ***	**99.1±7.9**	**93.3±4.1**	**105.7±8.6**
ESP (mmHg)	**85.8±11.1**	**97.5±18.1**	**86.1±7.4**	**96.7±23.9**	**81.7±7.4**
EDP (mmHg)	**13.33±1.2**	**13.2±4.9**	**13.9±2.7**	**26.5±9.2**	**7.3±1.9**

Border zone cardiomyocyte hypertrophy at 8 week post MI




A
Infarct area at 24 hrs post MI
% Infarct area in LV
0
10
20
30
40
X-Vivo
CM
antiTGFβ
antiIGF1
IgG
B
Infarct area at 8 wks post MI
% Infarct area in LV
0
10
20
30
40
50
**
*
X-Vivo
CM
antiTGFβ
antiIGF1
IgG

Effect of BMSC on Global EF



Janssens 2006

BMSC reduced infarct size by 30% at 4 mths post treatment

	Baseline		4 months		Difference		Treatment effect*	p
	Control (n=30)	BMSC (n=30)	Control(n=30)	BMSC (n=30)	Control (n=30)	BMSC (n=30)		
LVEDV index (mL/m²)	83·1 (14·7)	81·2 (14·0)	85·9 (19·5)	84·1 (20·8)	2·8 (15·0)	2·8 (15·2)	0·997 (0·915 to 1·086)	0·95
LVESV index (mL/m²)	44·4 (12·3)	42·2 (10·5)	45·0 (17·9)	41·0 (15·5)	0·6 (11·6)	−1·1 (11·2)	0·980 (0·861 to 1·115)	0·76
Global LVEF (%)	46·9 (8·2)	48·5 (7·2)	49·1 (10·7)	51·8 (8·8)	2·2 (7·3)	3·4 (6·9)	1·036 (0·961 to 1·118)	0·36
LV mass index (g/m²)	64·5 (15·8)	57·0 (11·0)	58·7 (11·1)	50·9 (9·6)	-5·8 (11/9)	−6·1 (6·8)	0·931 (0·864 to 1·003)	0·06
Late contrast enhancement (g)	22·3 (16·1)	20·6 (14·3)	14·7 (9·3)	10·3 (8·0)	-7·9 (8·5)	−10·2 (7·9)	0·717 (0·530 to 0·971)	0·036
Systolic wall thickening in infarct area (%)	21·8 (19·21)	23·6 (17·9)	23·7 (18·9)	29·3 (21·7)	1·9 (21·4)	5·7 (24·4)	4·99 (−5·3 to 15·3)	0·35
Systolic wall thickening in border zone (%)	32·7 (15·4)	36·6 (18·9)	38·4 (21·1)	40·8 (17·2)	5·7 (18·8)	4·2 (22·6)	−0·84 (-10·5 to 8·9)	0·87

LVEF=LV ejection fraction. Data in first six columns are mean (SD). *Expressed as ratios (BMSC/CONTROL) of adjusted means for all variables (ANCOVA) with 95% CIs, except for wall thickening where expressed as differences (BMSC−CONTROL) in adjusted means (ANCOVA) with corresponding 95% CIs.

Table 2: LV volume and mass indices, global and regional LV function, and late contrast enhancement 4 days after intracoronary infusion and at 4 months' follow-up

Infarct size significantly decreased by BMSC (28% treatment effect)

Janssens 2006

Conclusions

- Progenitor cell therapy has potent paracrine effects on at risk cardiomyocytes
- Effects are acute and chronic (both anti-apoptotic and cardiotrophic)
- Specific growth factors implicated acutely
- Border zone apoptosis may be novel therapeutic target in post AMI therapy
- Elucidation of relationship between acute and chronic effects necessary for therapy selection

Acknowledgements

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