



SOCIETÀ ITALIANA  
DI GERONTOLOGIA  
E GERIATRIA

# Il blocco del Vascular Endothelial Growth Factor (VEGF) previene gli effetti benefici della terapia con $\beta$ -bloccanti in un modello sperimentale di scompenso cardiaco

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«Federico II»**





- Attualmente lo scompenso cardiaco è la causa principale di morbidità e mortalità nei pazienti con infarto miocardico pregresso
- La perdita della funzionalità cardiaca dopo infarto miocardico induce : rimodellamento cardiaco, ipertrofia compensatoria e stimolazione della neoangiogenesi cardiaca.





- La terapia con  $\beta$ -bloccanti riduce le riospedalizzazioni e la mortalità (Bristow, M.R. 2000. Circulation).
- I  $\beta$ -bloccanti inibiscono l'ipertono simpatico, migliorano il rimodellamento cardiaco, riducono il consumo di  $O_2$ , riducono il rischio di aritmie, inibiscono la internalizzazione dei  $\beta$ -AR.





- I  $\beta$ -bloccanti migliorano la perfusione miocardica potenziando la neoangiogenesi nel cuore scompensato (Dedkov, E.I., et al 2005 Circ Physiol.; Ulu, N., et al 2009 Cardiovasc Pharmacol; Christensen, L.P., 2009 Am J Physiol)
- HRR attiva il VEGF ( Zheng, W., et al 1999 Circ Res)
- L'inibizione del signaling del VEGF è cruciale nella transizione da ipertrofia compensatoria a rimodellamento maladattivo (Shiojima, I., et al 2005 J Clin Invest)





## Lo scopo dello studio:

- Valutare gli effetti dell'inibizione dell'angiogenesi indotta dal  $\beta$ -bloccante.



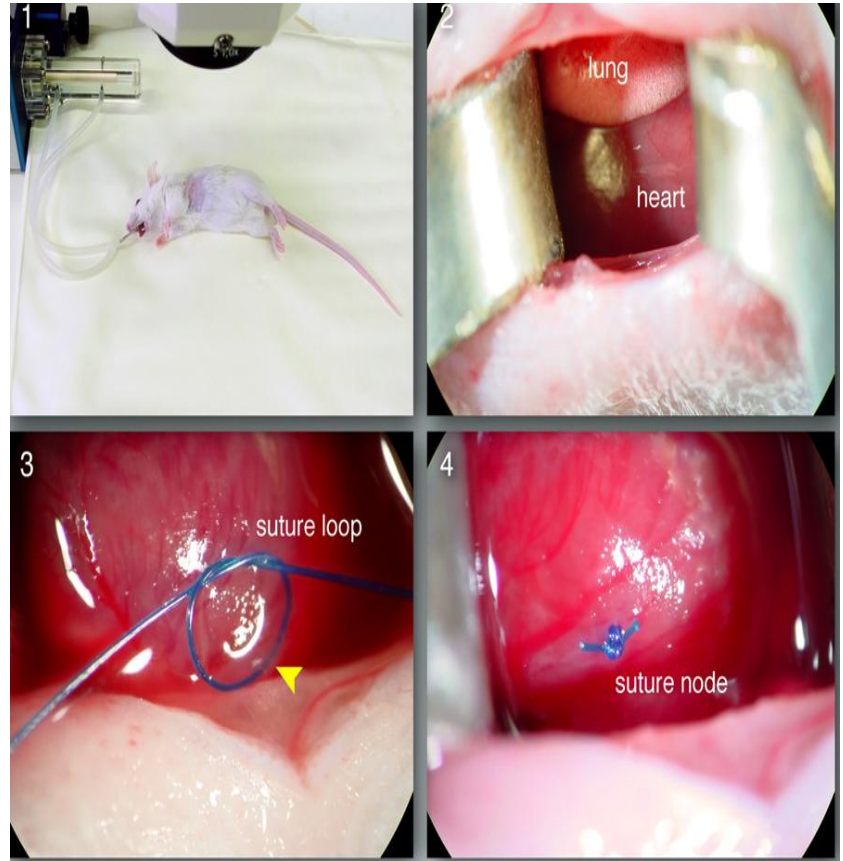
# Metodi



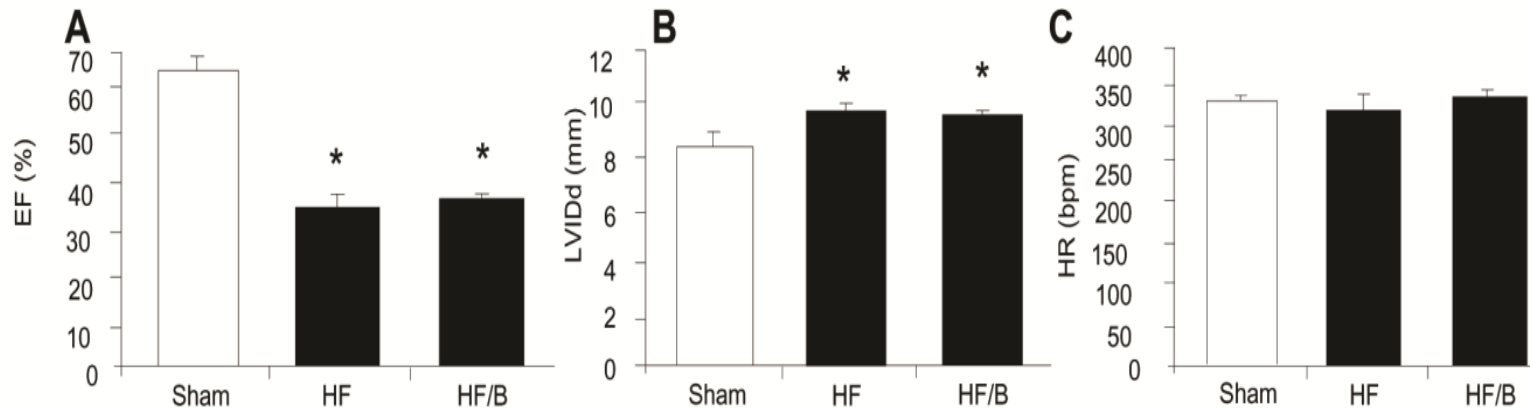
8 settimane  
dopo IM

placebo

bisoprololo



# Dati ecocardiografici a T0.



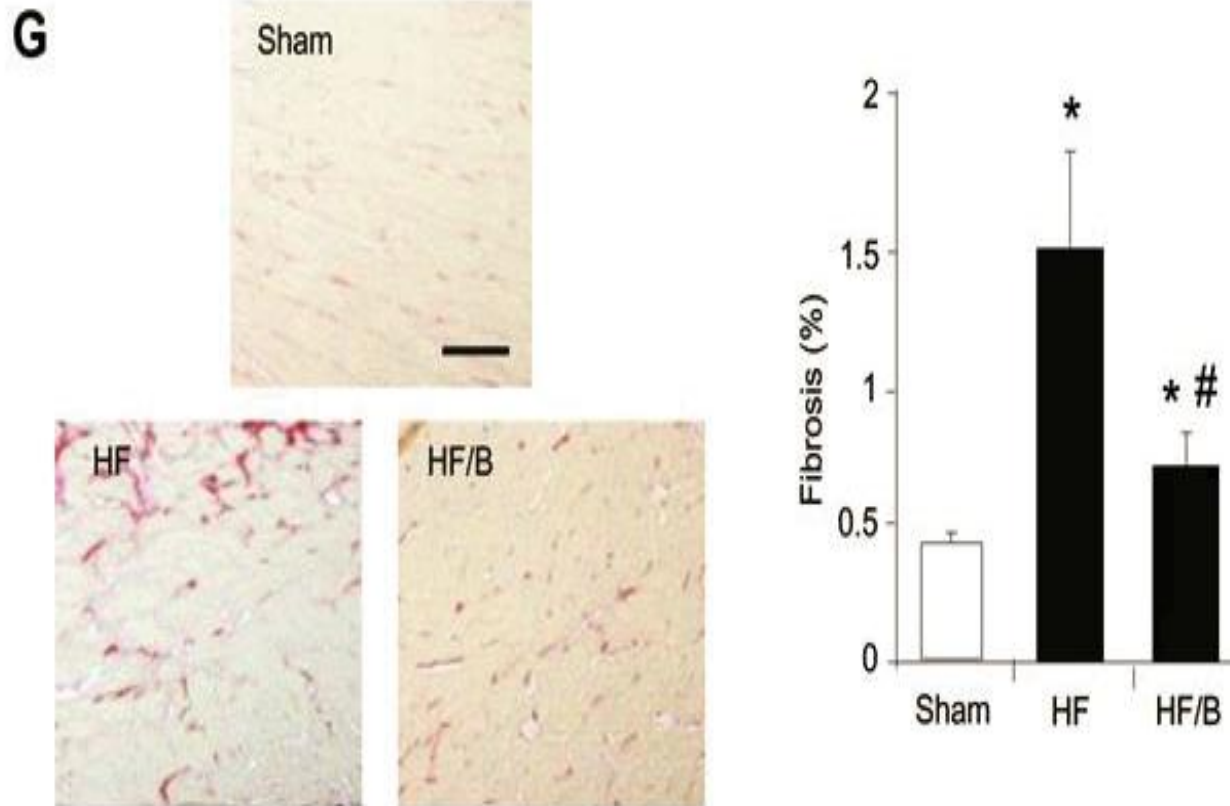
Left ventricular ejection fraction (EF), LV internal diameter at diastole LVIDd and Heart Rate measured by echocardiography at 8 weeks post MI before bisoprolol or placebo treatments initiation. (n=12) rats per group. Data are presented as mean  $\pm$  SEM. \*P<0.05 versus sham. One-way ANOVA analysis and Bonferroni test among all groups.

## Dati clinici ed ecocardiografici nei ratti sham e operati alla fine dello studio

	Sham	HF/control	HF/Bisoprolol
<b>Physical data</b>			
BW (kg)	$0.471 \pm 0.013$	$0.469 \pm 0.014$	$0.454 \pm 0.015$
HW (g)	$1.16 \pm 0.04$	$1.41 \pm 0.01^*$	$1.24 \pm 0.03^{*\dagger}$
HW/BW ( $\text{gxKg}^{-1}$ )	$2.48 \pm 0.08$	$3.01 \pm 0.09^*$	$2.73 \pm 0.08^{*\dagger}$
<b>Echocardiography</b>			
HR (bpm)	$321.5 \pm 15.9$	$324.8 \pm 7.1$	$268.8 \pm 7.7^{**}$
LV EF (%)	$64.8 \pm 0.7$	$27.9 \pm 1.9^*$	$36.7 \pm 1.4^{*\dagger}$
LVIDd (mm)	$8.5 \pm 0.2$	$11.0 \pm 0.4^*$	$9.9 \pm 0.2^{*\dagger}$
LVIDs (mm)	$5.4 \pm 0.1$	$9.4 \pm 0.4^*$	$8.1 \pm 0.2^{*\dagger}$
LVAWDd (mm)	$1.72 \pm 0.05$	$1.54 \pm 0.10^*$	$1.46 \pm 0.07^*$
LVPWDd (mm)	$1.72 \pm 0.07$	$1.91 \pm 0.10^*$	$2.22 \pm 0.08^{*\dagger}$
Infarct size (%)	-	$46.3 \pm 4.2$	$44.8 \pm 3.1$

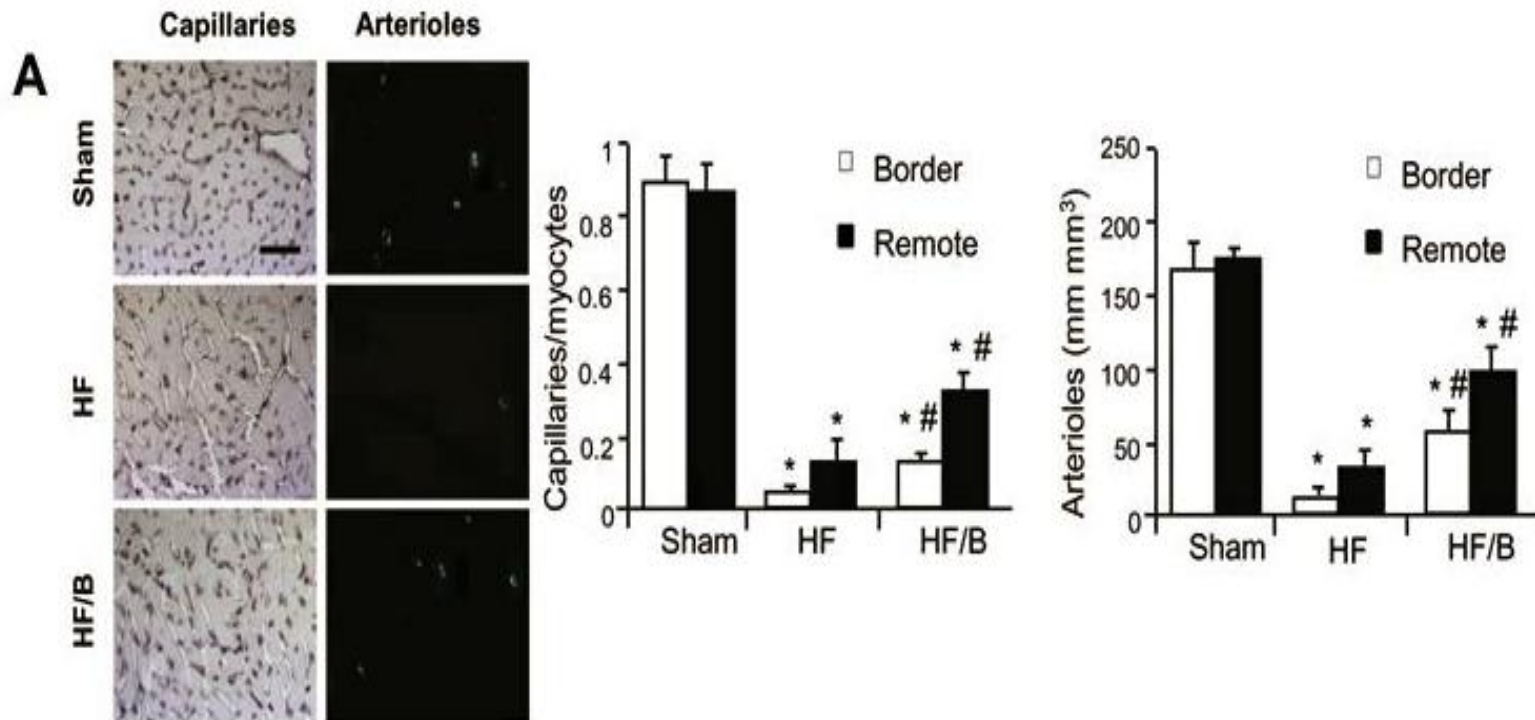


# L'effetto del bisoprololo sulla fibrosi cardiaca



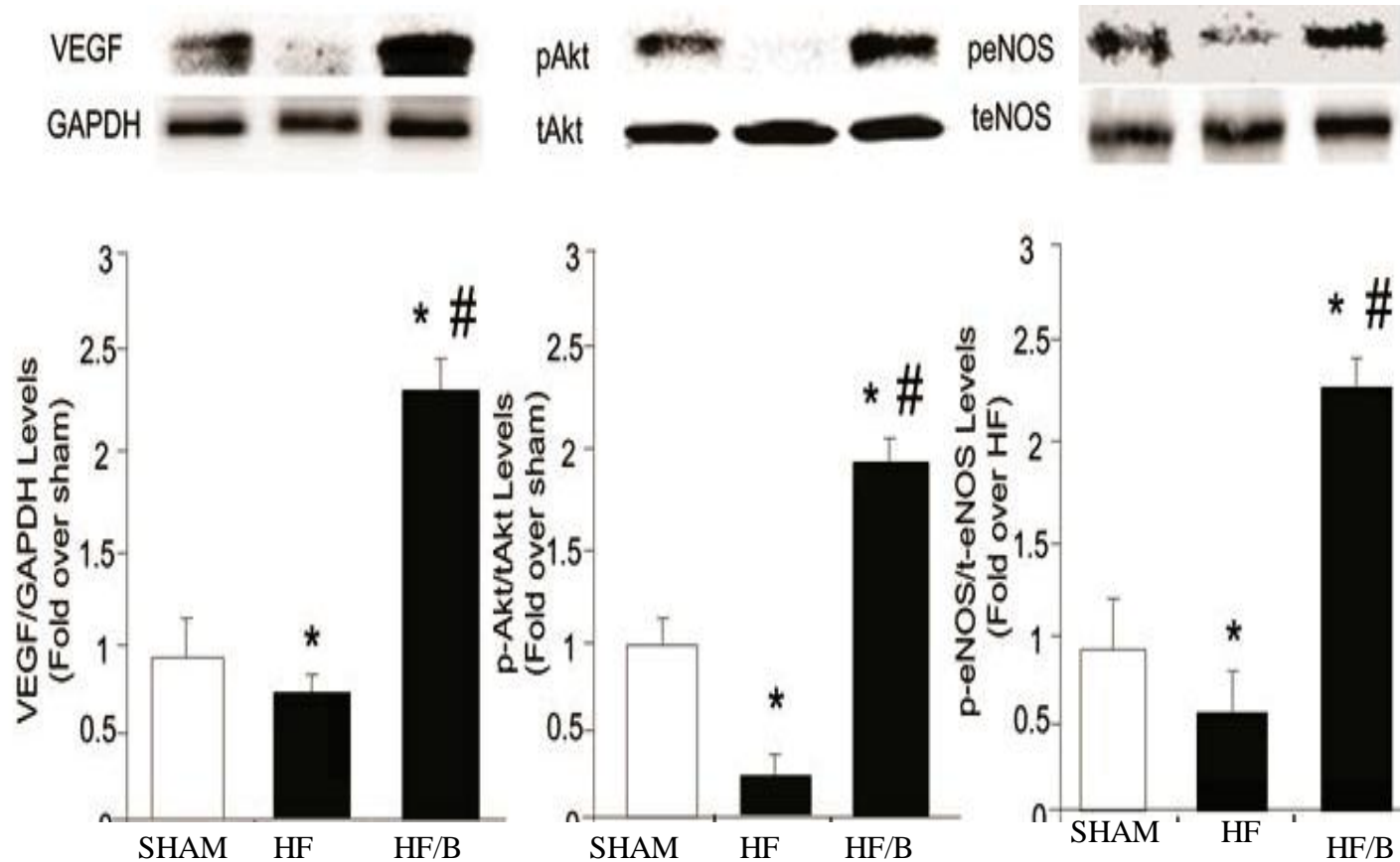
Fibrosis in cardiac section from all three experimental groups at the end of the study (n=5 for each group). Representative panels of micro-sirius red staining (magnification x200) and average quantitative analysis Scale bar: 50  $\mu$ m. Data are presented as mean  $\pm$  SEM. \*P<0.05 versus sham; #P<0.05 versus HF; P<0.05 versus HF. One- way ANOVA analysis with Benferroni test among all groups.

# L'effetto del bisoprololo sull'angiogenesi

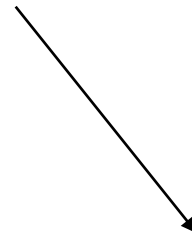
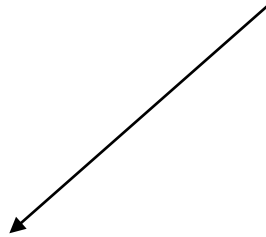
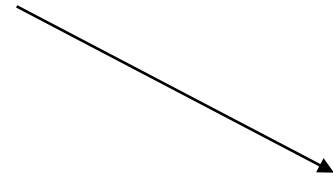
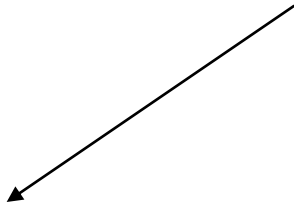


Effects of bisoprolol on cardiac capillary and arteriolar network. Representative images of Lectin Bandeiraea simplicifolia I staining of capillaries and arterioles stained with antibodies against smooth muscle  $\alpha$ -actin in cardiac section obtained from sham, HF and HF/B rats at the end of the study period in the lateral wall far from the infarcted area (remote). Bar graphs show data on capillary counts and arteriolar length density in either border or remote zones in all study period. (n=5 rats per group and 5 sections per animal).

# L'espressione cardiaca di VEGF, pAkt e peNOS



Cardiac protein expression of VEGF, p-Akt, and peNOS in sham, HF, HF/B at the end of the study. The expression of GAPDH was used as an internal control to normalize VEGF levels. p-Akt to total p-Akt ratio, and peNOS to total peNOS ratio indicated respectively the levels of Akt and eNOS phosphorylation in the heart (n=5 hearts per group). Data are presented as mean  $\pm$  SEM. \*P<0.05 versus sham; #P<0.05 versus HF. One-way ANOVA analysis with Benferroni test among all groups.



Placebo e Ad-Ctrl

Bisoprololo e Ad-Flk

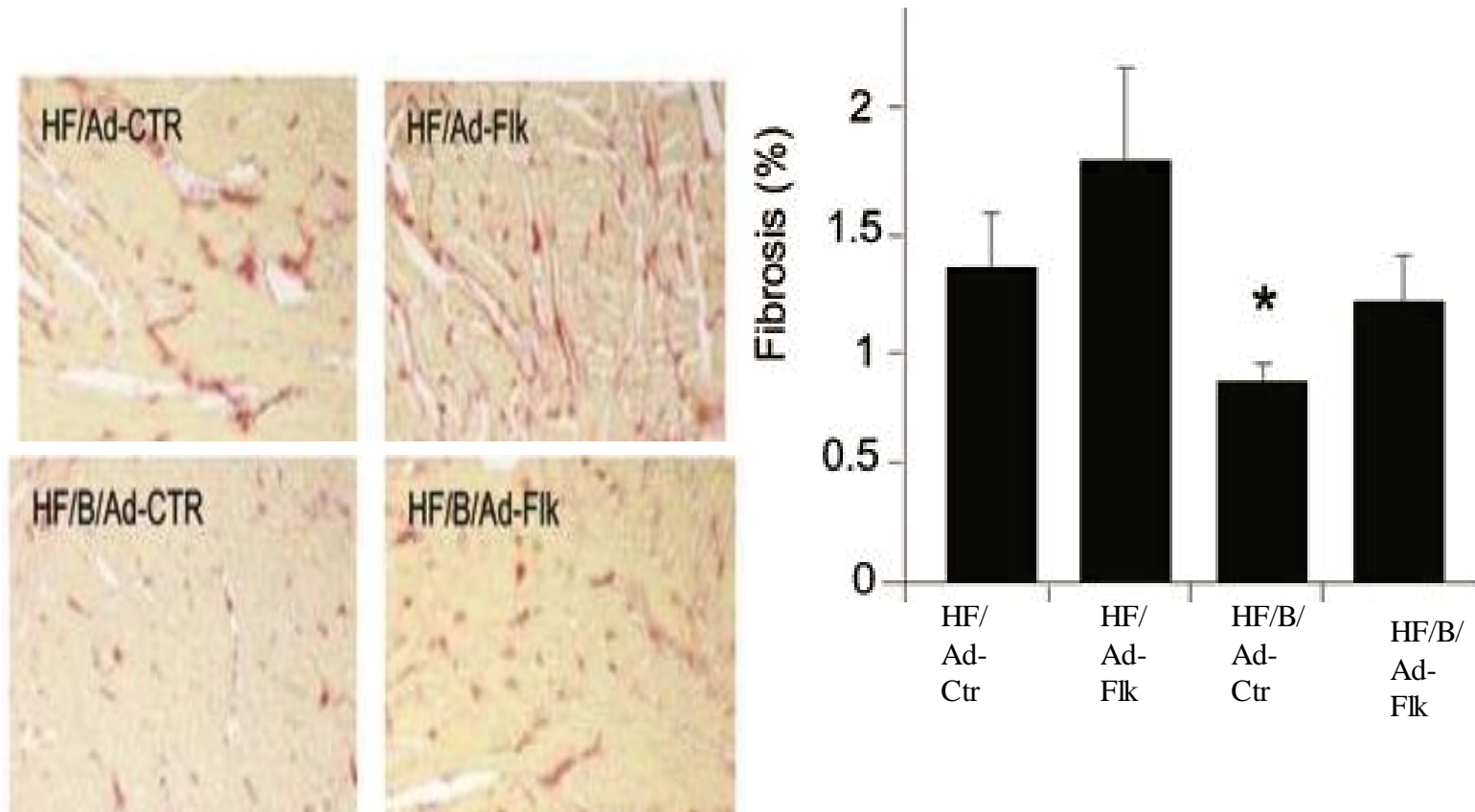
Placebo e Ad-Flk

Bisoprololo e Ad-Ctrl

## Dati clinici e ecocardiografici nei ratti scompensati alla fine dello studio

	HF/AdCTR	HF/AdFlk	HF/B/AdCTR	HF/B/AdFlk
<b>Physical data</b>				
BW (kg)	0.457±0.019	0.468±0.017	0.460±0.016	0.459±0.013
HW (g)	1.50±0.06	1.43±0.04	1.22±0.09*	1.40±0.08
HW/BW (gxKg <sup>-1</sup> )	3.29±0.15	3.06±0.11	2.76±0.09*	3.05±0.12
<b>Echocardiography</b>				
HR (bpm)	334.4±13.2	317.0±13,2	274.0±4.1†	276.5±11.3†
LV EF (%)	27.3±0.9	24.3±1.8	36.1±0.7*	26.0±1.6
LVIDd (mm)	10.7±0.3	11.0±0.2	9.8±0.2*	10.9±0.2
LVIDs (mm)	9.3±0.3	9.7±0.3	7.9±0.2*	9.7±0.1
LVAWDd (mm)	1.37±0.11	1.42±0.08	1.51±0.08	1.40±0.15
LVPWDd (mm)	1.87±0.21	2.05±0.08	2.35±0.10*	2.07±0.12
Infarct size (%)	47.6±5.2	45.3±3.8	48.1±4.6	44.1±4.2

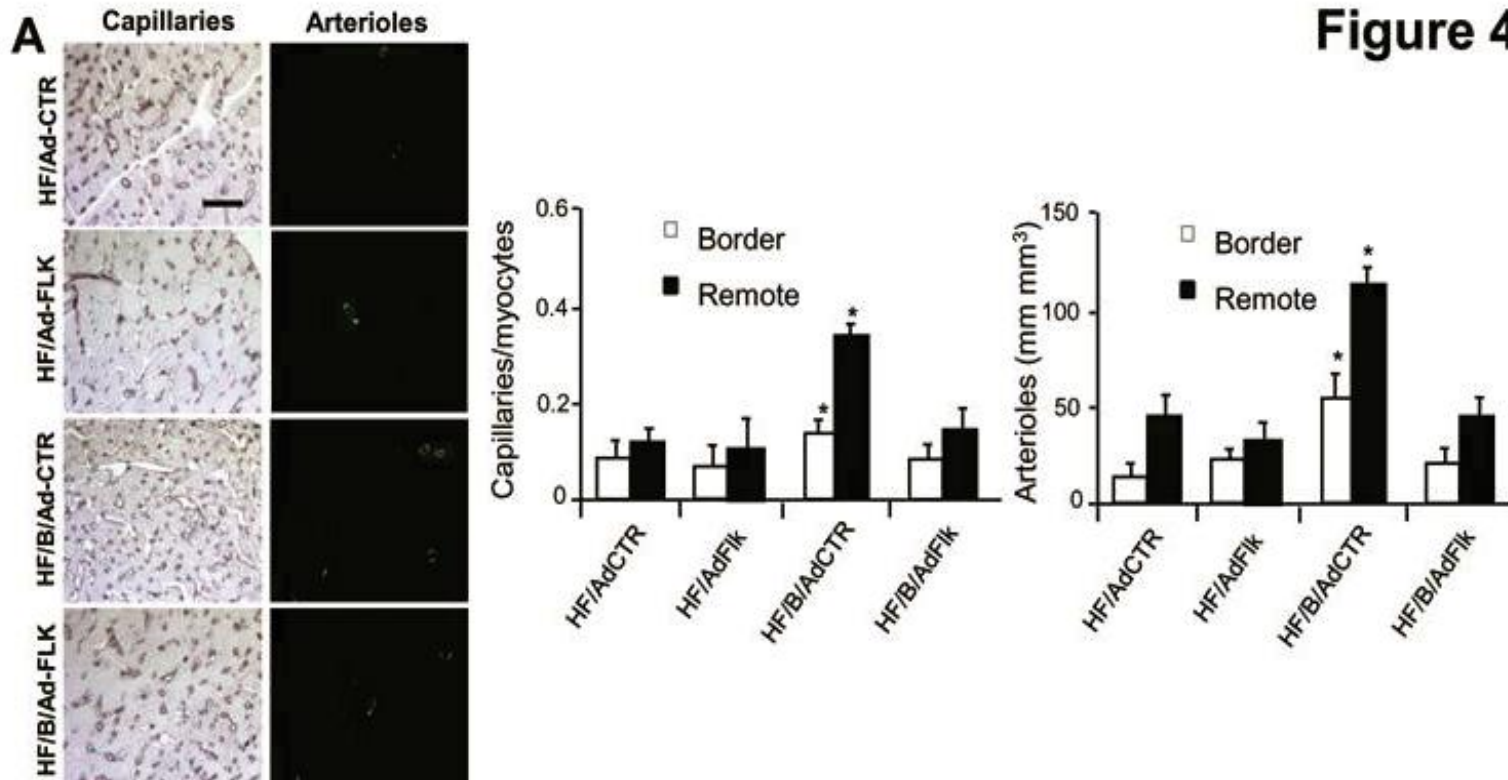
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Fibrosis in cardiac section from all four experimental groups at the end of the study (n=5 for each group). Representative panels of picro-sirius red staining (magnification x200) and average quantitative analysis Scale bar: 50  $\mu$ m. Data are presented as mean  $\pm$  SEM. \*P<0.05 versus all other HF groups. One-way ANOVA analysis with Benferroni test among all groups.

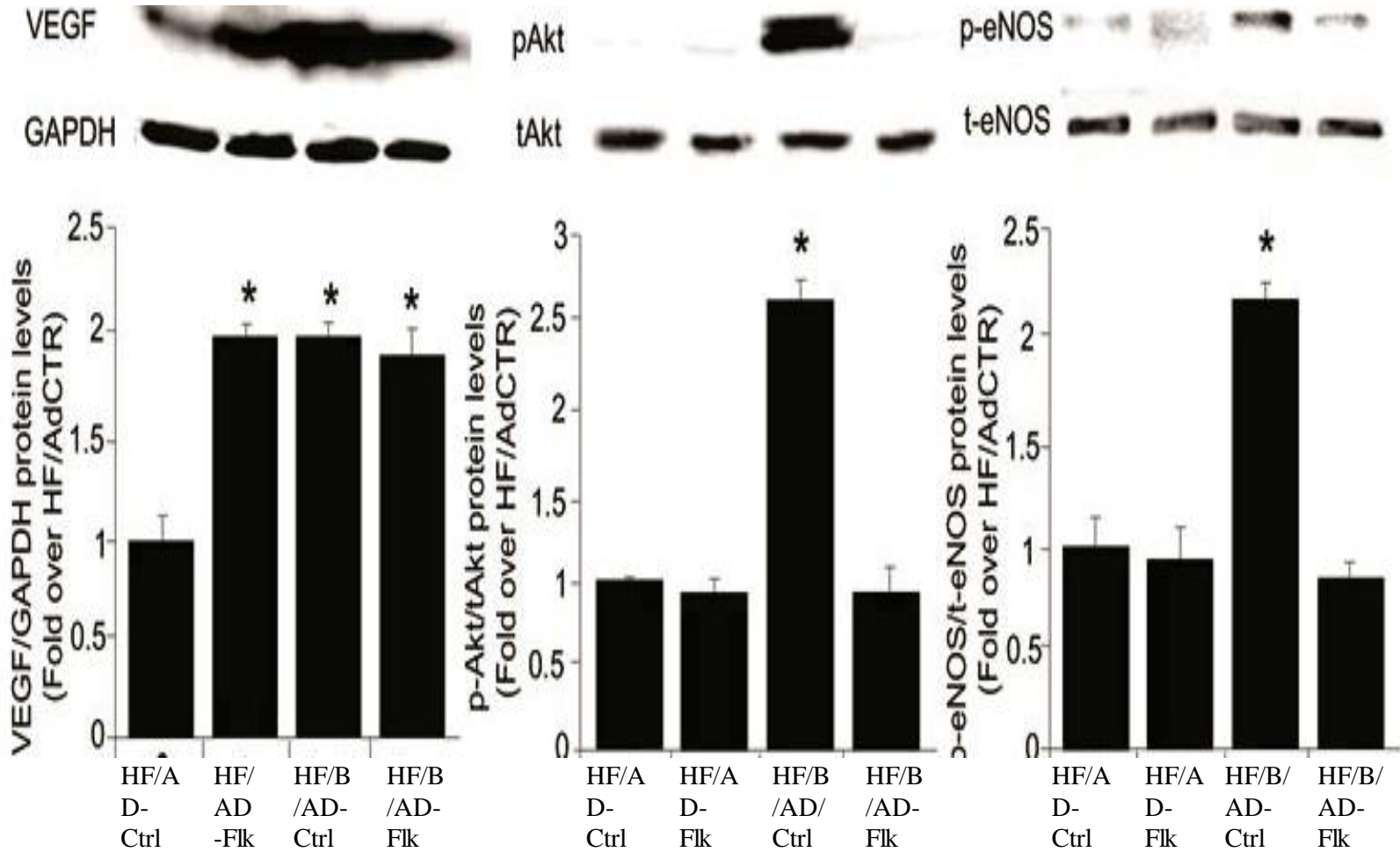
# L'effetto del bisoprololo e dell'inibizione del VEGF sull'angiogenesi.

**Figure 4**



Effects of bisoprolol on cardiac capillary and arteriolar network. Representative images of Lectin *Bandeiraea simplicifolia* I staining of capillaries and arterioles stained with antibodies against smooth muscle  $\alpha$ -actin in cardiac section obtained from sham, HF and HF/B rats at the end of the study period in the lateral wall far from the infarcted area (remote). Bar graphs show data on capillary counts and arteriolar length density in either border or remote zones in all study period. (n=5 rats per group and 5 sections per animal. Data are presented as mean  $\pm$  SEM. \*P<0.05 versus all other HF groups.

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# Conclusioni

- La terapia con  $\beta$ -bloccante induce la neoangiogenesi nel cuore scompensato attraverso l'attivazione del signaling del VEGF
- L'effetto proangiogenico del  $\beta$ -bloccante è essenziale per gli effetti terapeutici sulla funzione ed il rimodellamento cardiaco.





Grazie!!!

