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NO REFLOW

Imanol Otaegui

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Generalitat de Catalunya Departament de Salut

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Myocardial ischemia

When ischemia develops, oxidative metabolism stops and anaerobic glycolysis supersedes,

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increasing lactate, H+, ammonium, degraded nucleotide phosphates, G6P,

increasing the osmotic load

that leads to cellular swelling and interstitial edema.

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Reperfusion-related injury

One of the earliest events that develop following blood flow restoration to ischemic myocardium is exacerbation of ischemia-initiated interstitial and cellular edema.

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Myocardial wall thickening after reperfusion

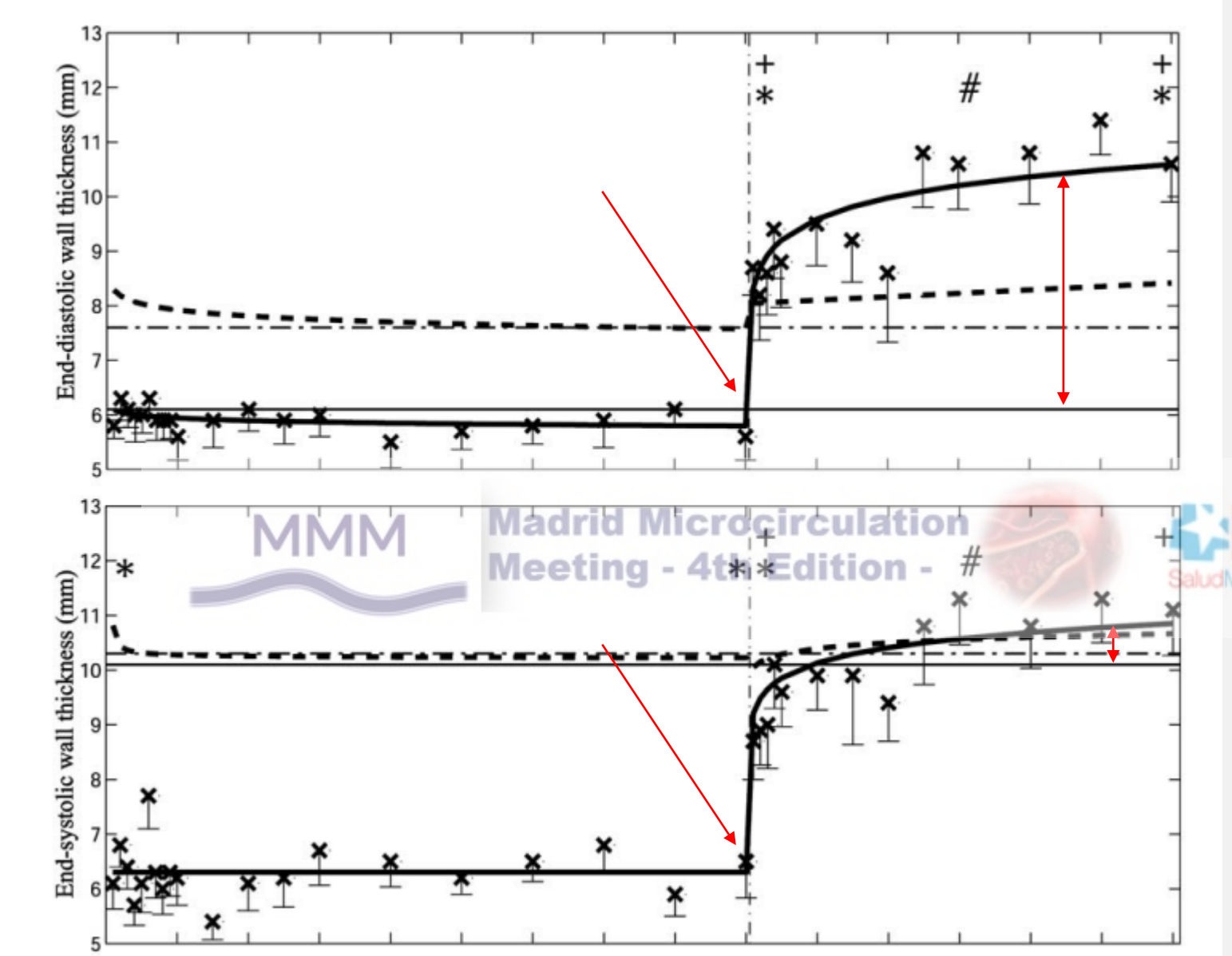

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Fig. 4 Temporal evolution of the end-diastolic (top), end-systolic (middle) and post-systolic (bottom) wall thickness of the "at risk" posterior wall segment (crosses).... the the thin horizontal solid line represents the baseline value

Turschner O, D'hooge J, Dommke C, Claus P, Verbeken E, De Scheerder I, Bijnens B, Sutherland GR. The sequential changes in myocardial thickness and thickening which occur during acute transmural infarction, infarct reperfusion and the resultant expression of reperfusion injury. Eur Heart J. 2004 May;25(9):794-803. doi: 10.1016/j.ehj.2004.01.006. PMID: 15120891.

Endothelial Cell swelling

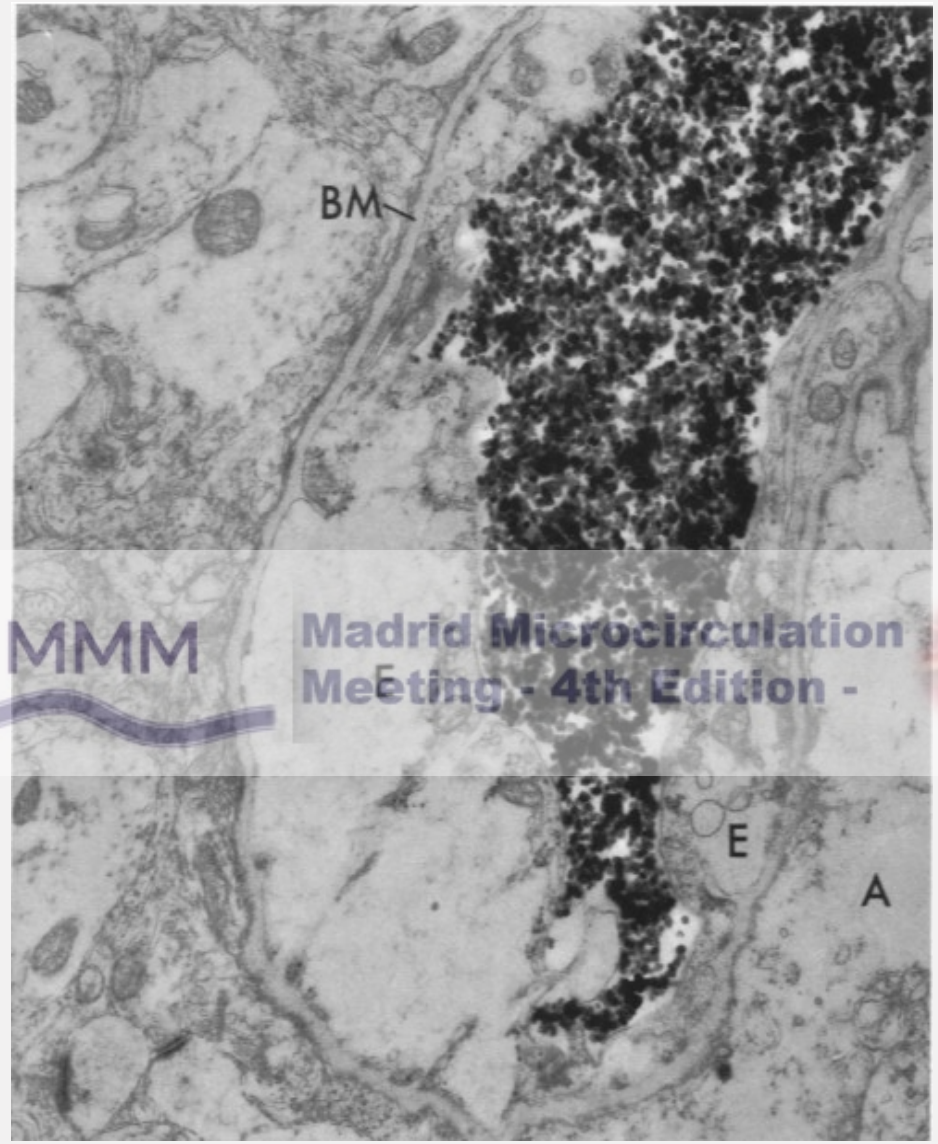

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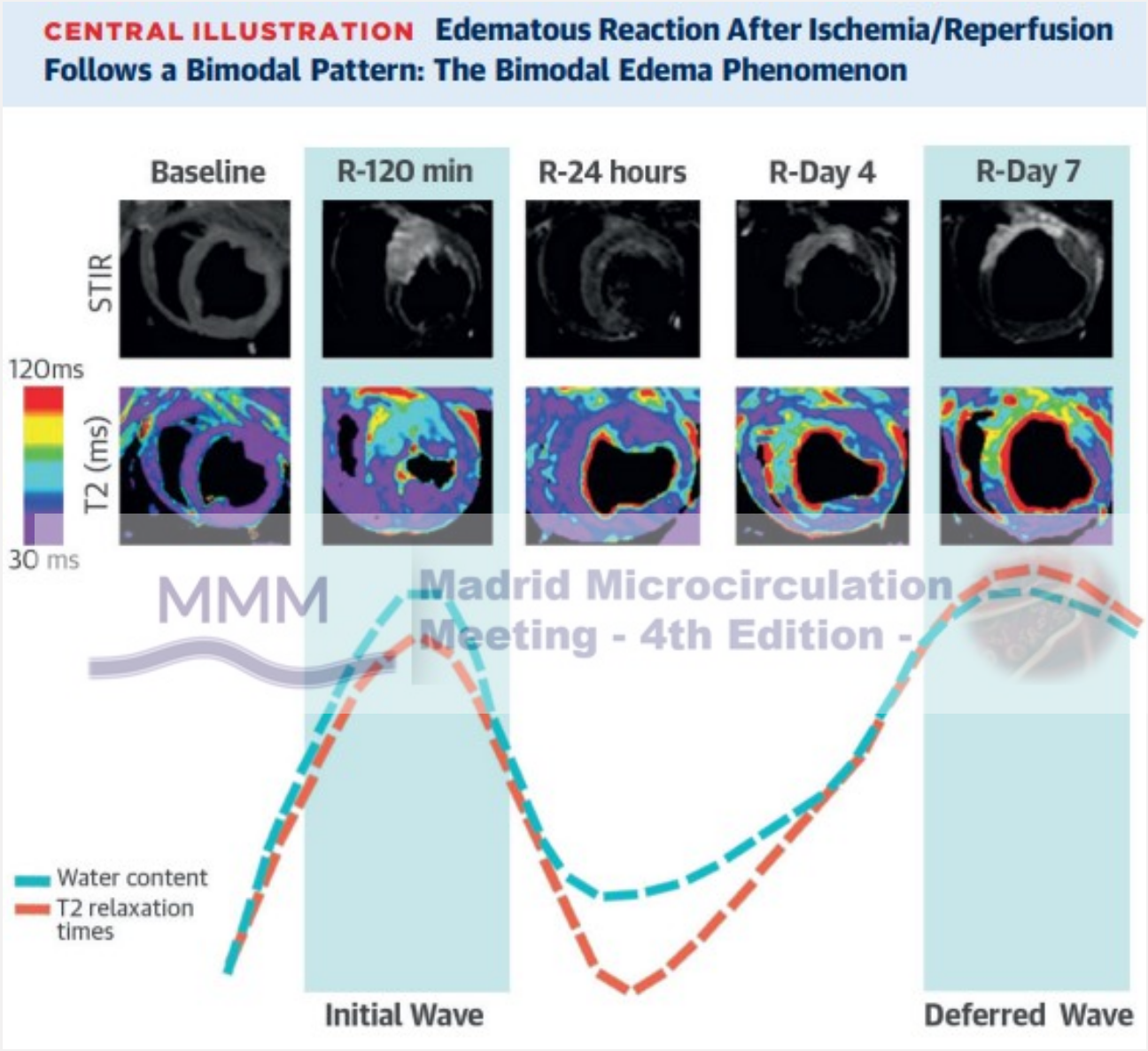
Fig. 21. Endothelial swelling in cerebral capillary (15 min. of ischemia, fixation by per- fusion 30 min. later). **Overhydrated endothelial cells (E)** bulge into lumen, which is filled with carbon black. There is no evidence that carbon is being spilled extravascularly, or that it has reached basement membrane (BM). Note also some astrocytic swelling (A).

Chiang J, Kowada M, Ames A 3rd, Wright RL, Majno G. Cerebral ischemia. III. Vascular changes. Am J Pathol. **1968** Feb;52(2):455-76. PMID: 5635862; PMCID: PMC2013336.



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Fernández-Jiménez R, Sánchez-González J, Agüero J, García-Prieto J, López-Martín GJ, García-Ruiz JM, Molina-Iracheta A, Rosselló X, Fernández-Friera L, Pizarro G, García-Álvarez A, Dall'Armellina E, Macaya C, Choudhury RP, Fuster V, Ibáñez B. Myocardial edema after ischemia/reperfusion is not stable and follows a bimodal pattern: imaging and histological tissue characterization. J Am Coll Cardiol. 2015 Feb 3;65(4):315-323. doi: 10.1016/j.jacc.2014.11.004. Epub 2014 Nov 17. Erratum in: J Am Coll Cardiol. 2018 Apr 17;71(15):1713. PMID: 25460833.

Myocardial Edema After Ischemia / Reperfusion Is Not Stable and Follows a Bimodal Pattern

The development of myocardial edema is a well-known phenomenon occurring after ischemia/reperfusion (myocardial infarction). This edematous reaction was long assumed to be stable for at least 1 week, but the post-ischemia/reperfusion phase was not previously tracked in a comprehensive serial study. In the present study, analysis of advanced cardiac magnetic resonance and histopathology showed that post-ischemia/reperfusion edema is bimodal. **An initial wave of edema abruptly appears upon reperfusion and almost completely disappears at 24 h**. A deferred wave appears later and increases progressively until day 7. STIR ¼ short-tau inversion recovery

Reperfusion-related injury

The early wave of edema appears to be due to exposure of a hyperosmotic interstitium (due to accumulation of catabolites produced during ischemia) to normo-osmotic blood at reperfusion.

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The Journal of Clinical Investigation

The "No-Reflow" Phenomenon after Temporary Coronary Occlusion in the Dog

Robert A. Kloner, … , Charles E. Ganote, Robert B. Jennings

J Clin Invest. 1974;54(6):1496-1508. https://doi.org/10.1172/JCI107898.

Reperfusion related injury

After 40 min of ischemia followed by reperfusion fluorescent dye thioflavin S managed to penetrate ischemic myocardium.

But if ischemia was prolongued for 90 min followed by reperfusion, thioflavin S failed to penetrate the ischemic myocardium and perfusion defects were observed in subendocardium.

Reperfusion failure was observed within seconds of clamp release, and it was well established within the first few minutes

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Reperfusion related injury

Myocardial cell swelling was prominent after both 40- and 90-min periods of ischemia, whereas capillary damage was most severe after 90 min of ischemia and was localized to areas of no reflow

Myocardial cells in areas with intact circulation showed massive swelling and formation of large contraction bands

Diffuse endothelial swelling (as opposed to localized protrusions) rarely was seen in dog heart.

Thus, the results suggested that capillary damage is a major contributing factor to the development of the no-reflow phenomenon.

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Reperfusion related injury

Capillary damage consisted in

- decreased numbers of pinocytotic vesicles,
- nuclear chromatin clumping
- and large protrusions of endothelial cytoplasm into the vascular lumen.

Endothelial protrusions and intraluminal membrane-bound bodies often filled the capillaries to a point that the lumen was obliterated

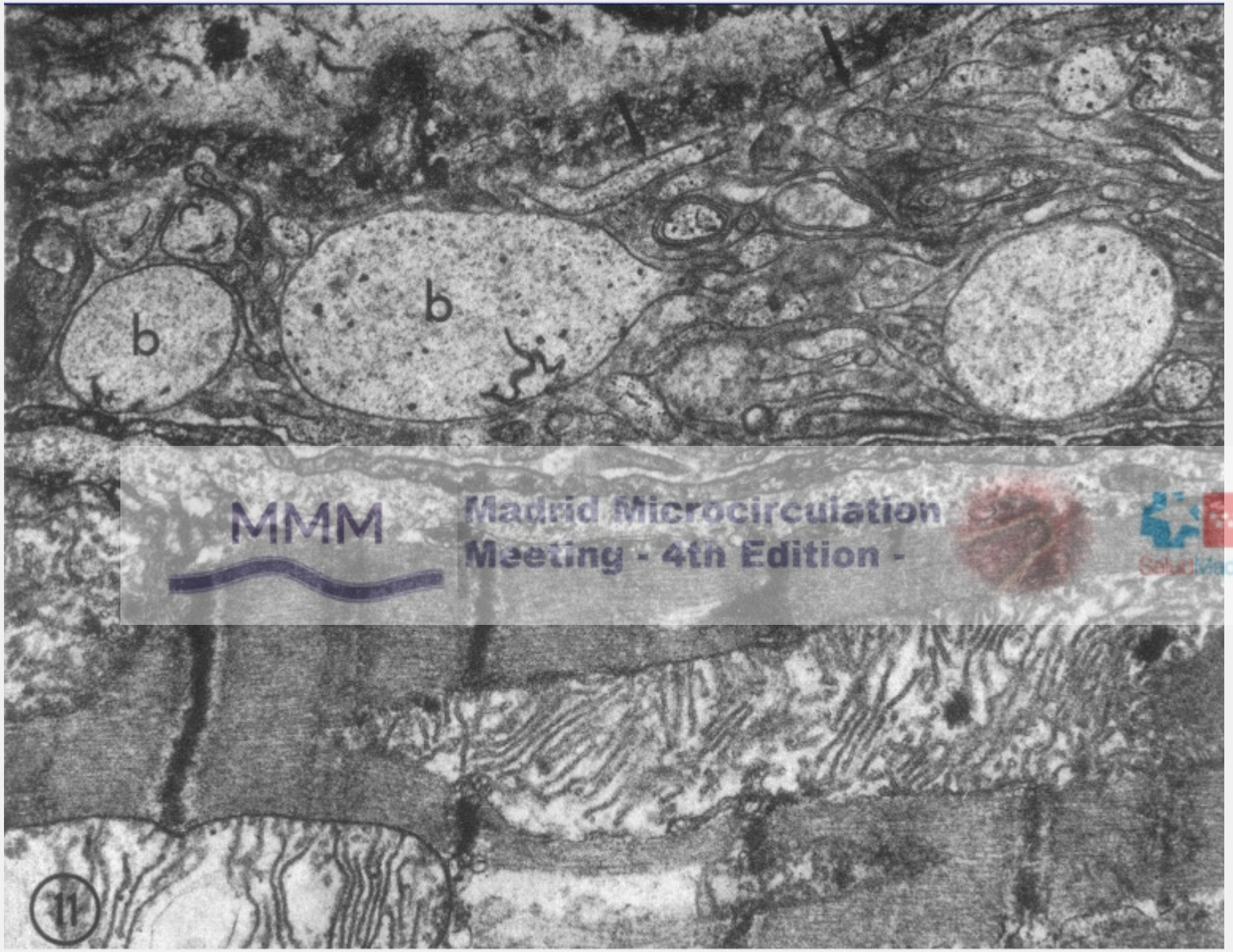

FIGURE 11. Temporarily ischemic for 90 min with 10-12 s of coronary blood reperfusion (from area of no reflow). Endothelial pinocytotic vesicles are sparse. The capillary lumen is full of endothelial protrusions (arrows) and membrane-bound bodies (b), some of which might represent degranulated platelets. Mitochondria are swollen with amorphous matrix dense bodies. I bands and intermyofibrillar edema are present. X 22,640.

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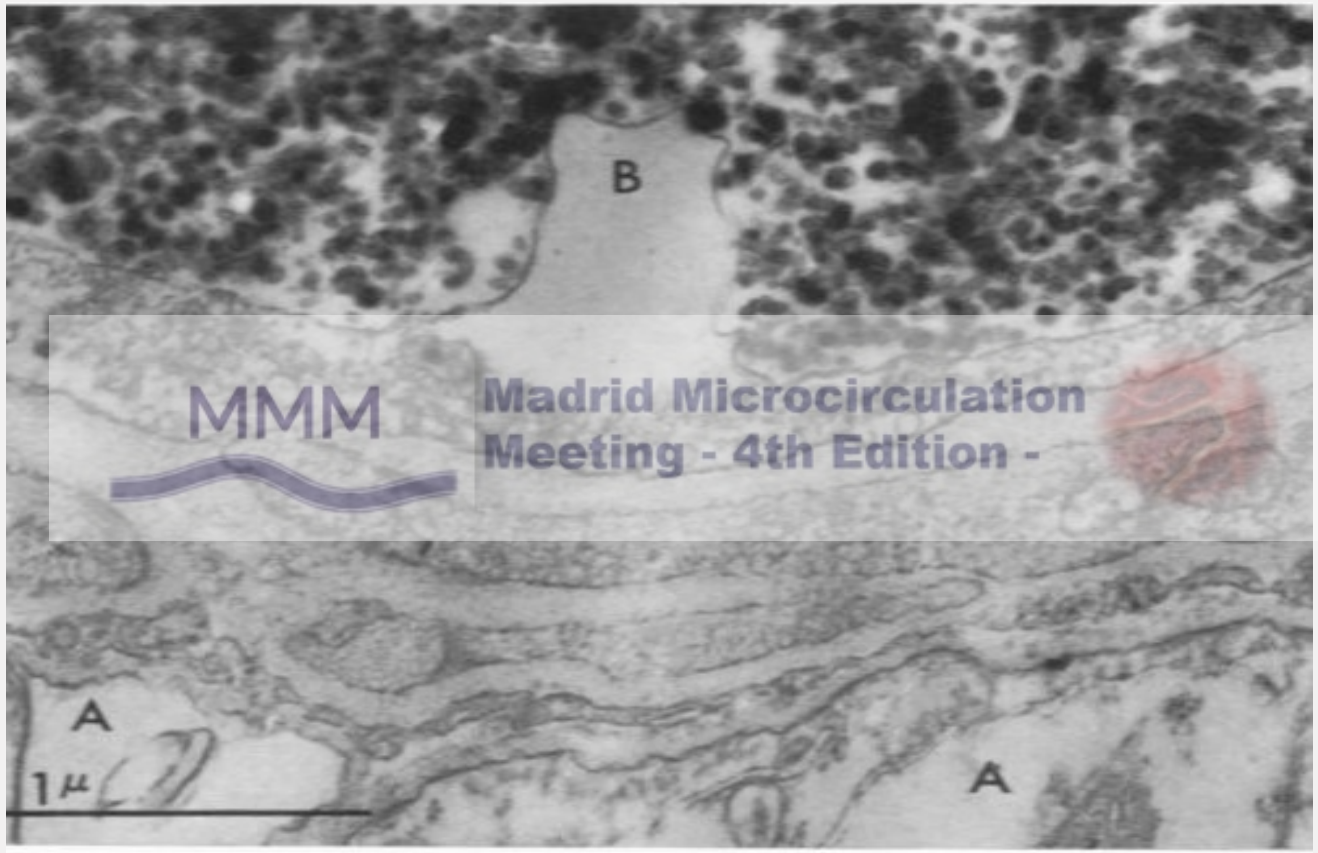
Kloner RA, Ganote CE, Jennings RB. The "no-reflow" phenomenon after temporary coronary occlusion in the dog. J Clin Invest. 1974 Dec;54(6):1496-508. doi: 10.1172/JCI107898. PMID: 4140198; PMCID: PMC301706.

Blebs



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Fhg. 20. Bleb (B) arising from surface of endothelial cell in venule. Cell membrane is continuous all around bleb; endothelial vesicles and other organelles seem to be excluded from this structure. There is some astrocytic swelling (A). Lumen is full of carbon particles.

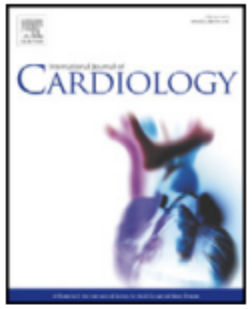
Chiang J, Kowada M, Ames A 3rd, Wright RL, Majno G. Cerebral ischemia. III. Vascular changes. Am J Pathol. 1968 Feb;52(2):455-76. PMID: 5635862; PMCID: PMC2013336.

International Journal of Cardiology 177 (2014) 935–941

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



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Intracoronary injection of adenosine before reperfusion in patients with ST-segment elevation myocardial infarction: A randomized controlled clinical trial☆

David Garcia-Dorado [a,*,1], Bruno García-del-Blanco [a,1], Imanol Otaegui [a,1], José Rodríguez-Palomares [a,1], Victor Pineda [b,1], Federico Gimeno [c,1], Rafael Ruiz-Salmerón [d,1], Jaime Elizaga [e,1], Arturo Evangelista [a,1], Francisco Fernandez-Avilés [e,1], Alberto San-Román [c,1], Ignacio Ferreira-González [a,f,1]

[a] Cardiology Department, Vall d'Hebron Hospital, Universitat Autónoma de Barcelona, Barcelona, Spain
[b] Institute for Diagnostic Imaging (IDI), Vall d'Hebron Hospital, Barcelona, Spain
[c] Institute for Heart Science (ICICOR), Clinic University Hospital of Valladolid, Valladolid, Spain
[d] Cardiology Department, University Hospital Virgen de la Macarena, Seville, Spain
[e] Cardiology Department, University General Hospital Gregorio Marañón , Department of Cardiology, Madrid, Spain
[f] Research Center for Epidemiology and Public Health of the Carlos III Health Institute (CIBERESP), Spain

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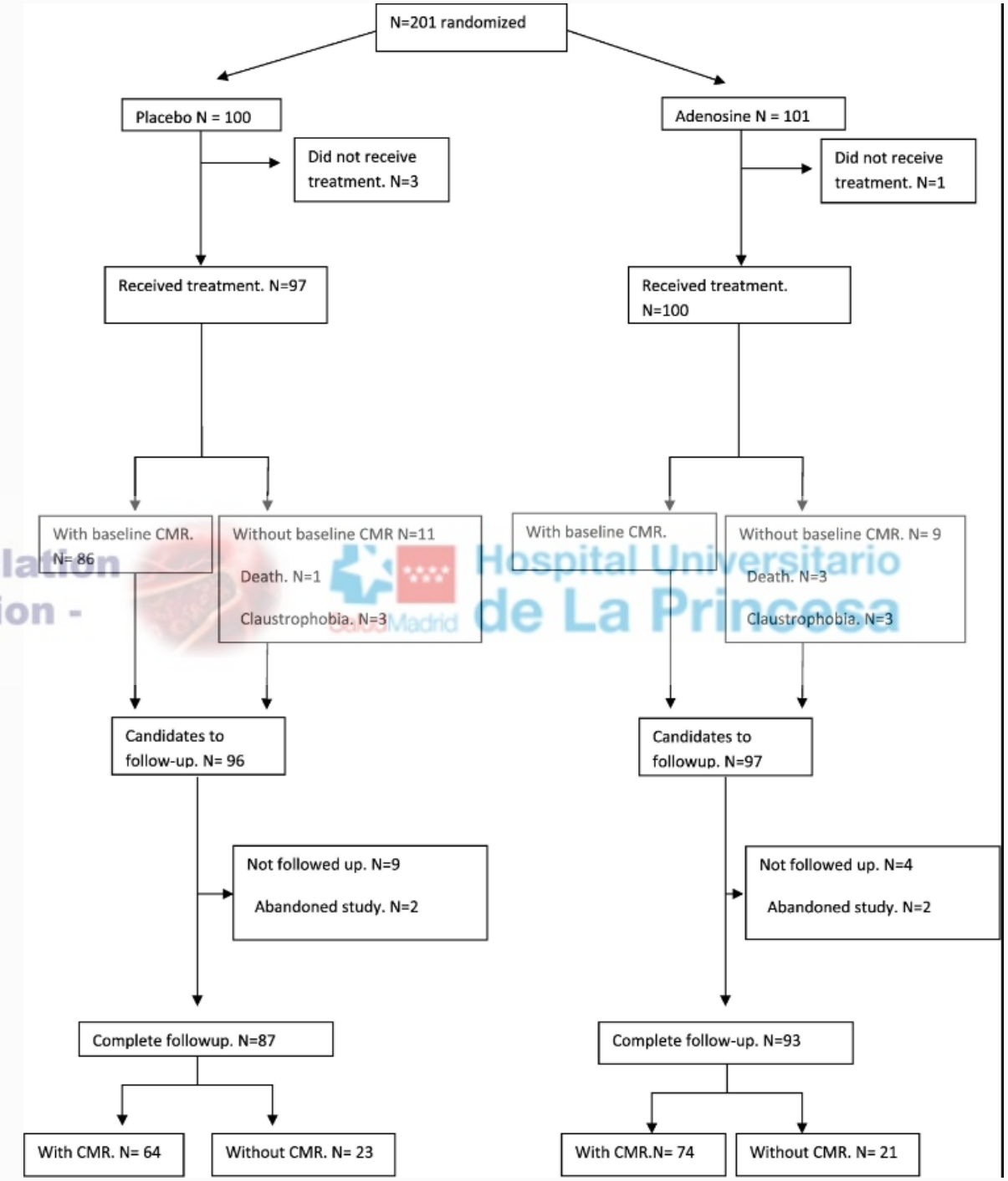
PROMISE TRIAL



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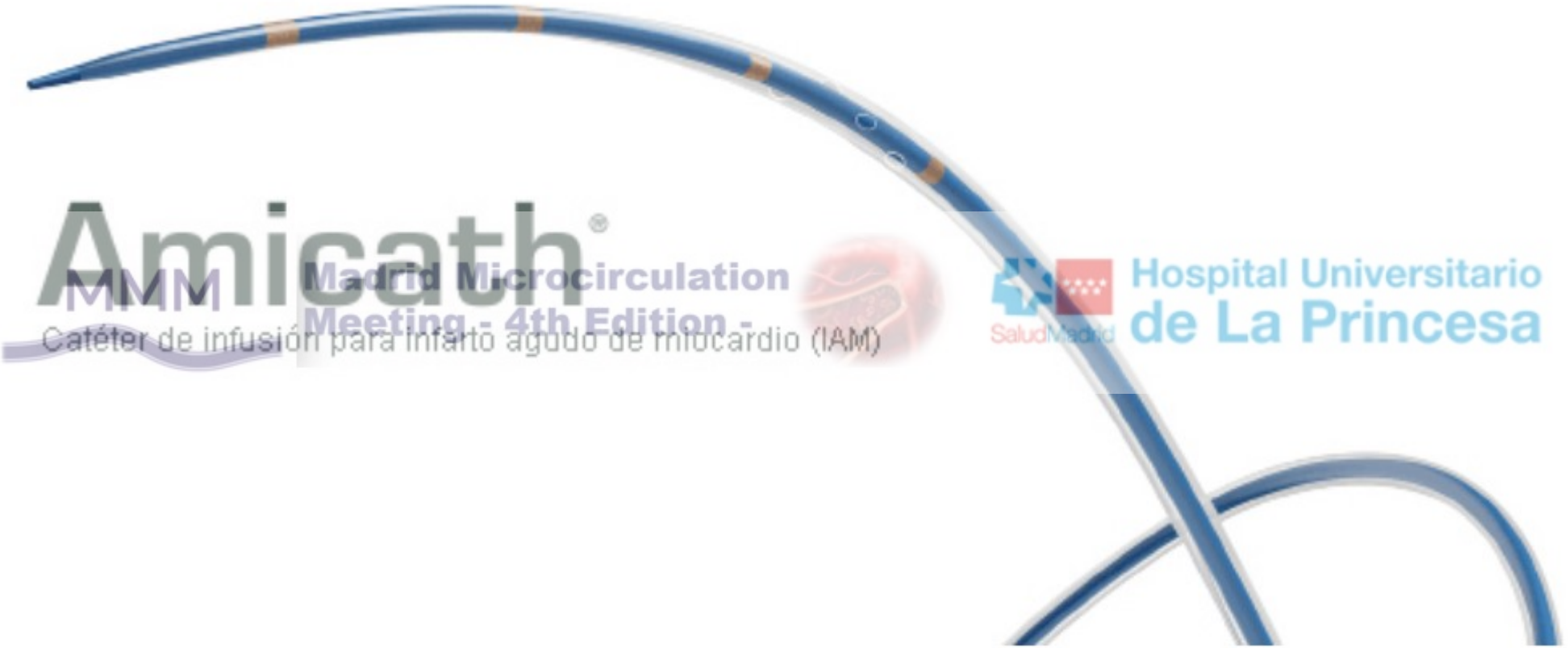

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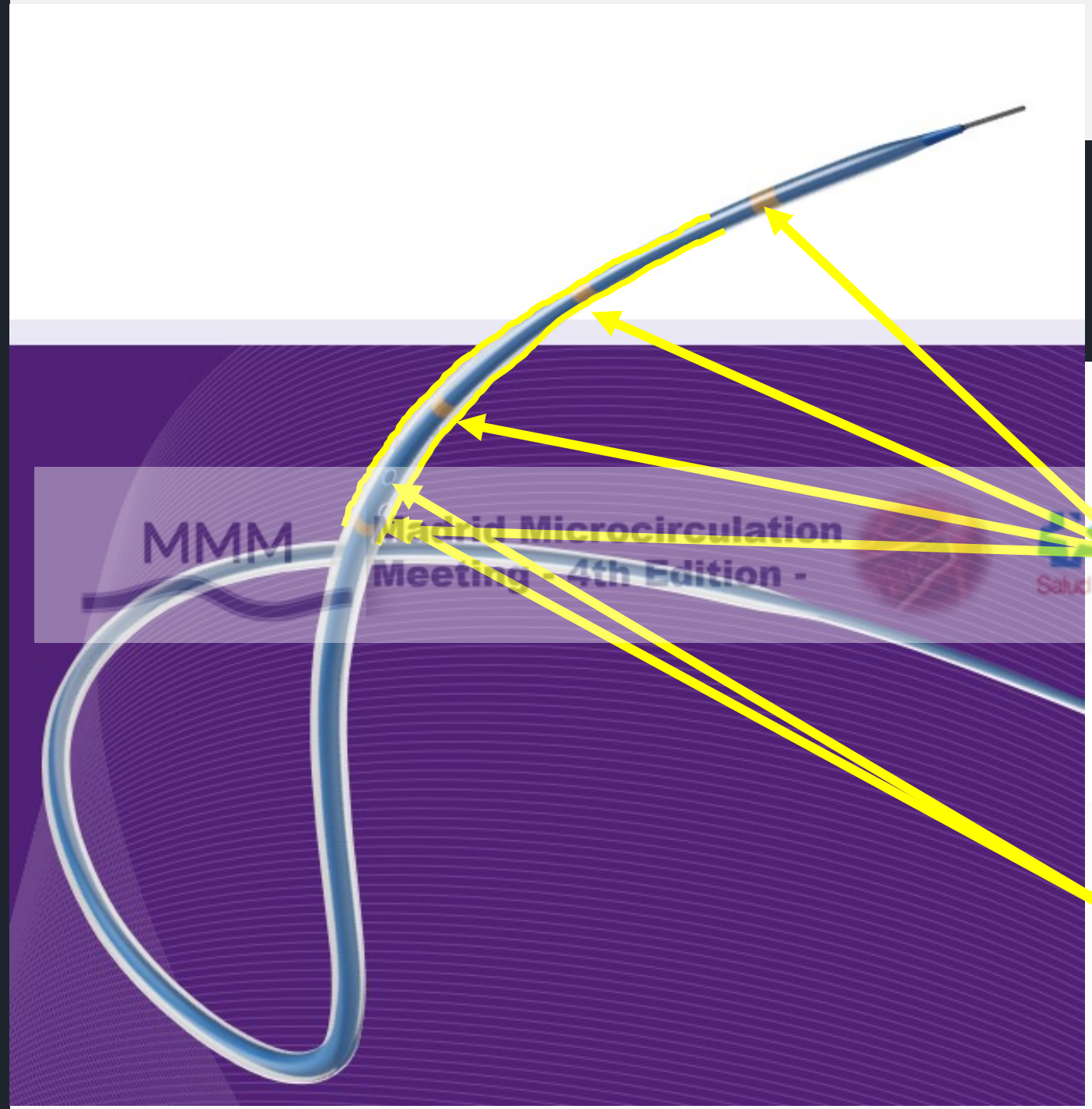
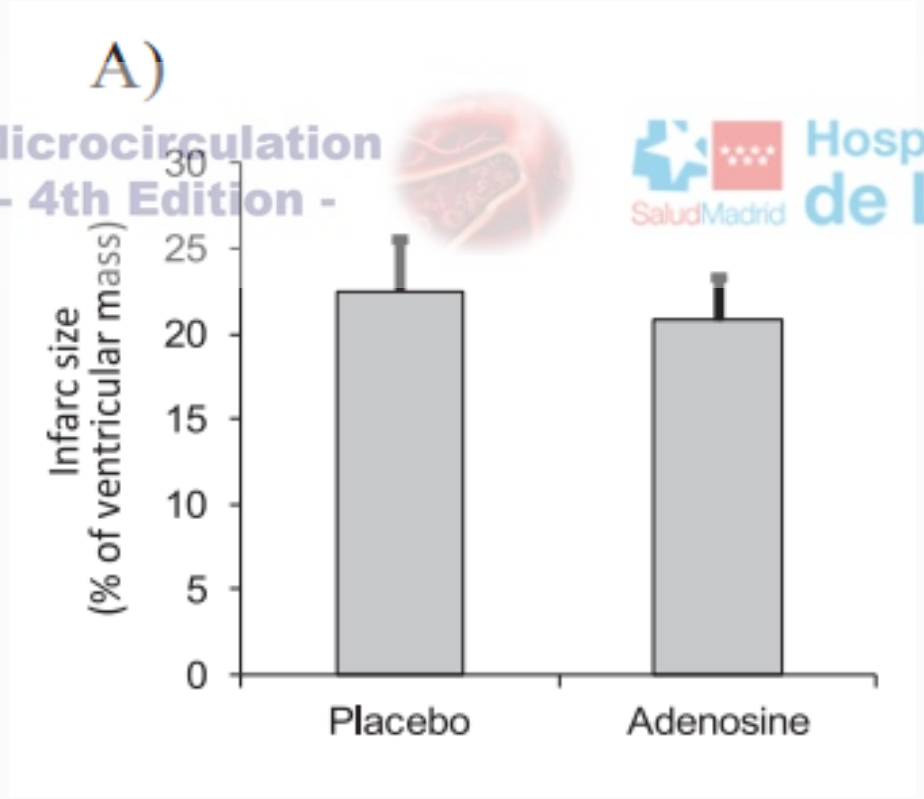


4 markers at 1 cm distant each

Progressive profile for Dotter effect mechanical thrombolysis

4 side holes for high flow injection, between the 3rd and 4th markers

Primary end point



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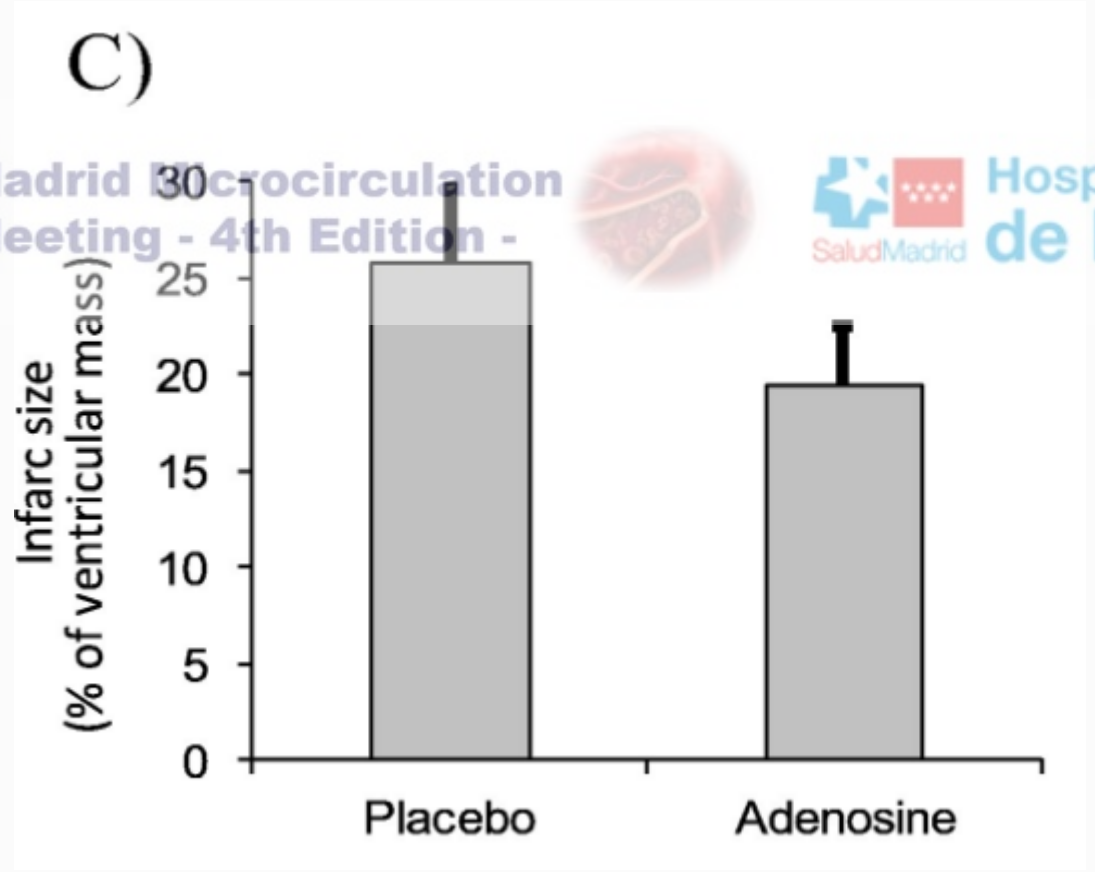
Prespecified subgroup <200 min



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Primary end point. Prespecified groups

	Placebo		Adenosine		P	p for interaction
	N	Mean (SD)	N	Mean (SD)		
Time onset-symptoms TIMI 3 flow						
Percentage of total necrotic myocardial mass						
Baseline						0.031
Less than 200 min	36	25.73±17.02	49	19.42±11.36	0.04	
Higher than 200 min	49	19.89±10.87	39	22.3±13.29	0.35	

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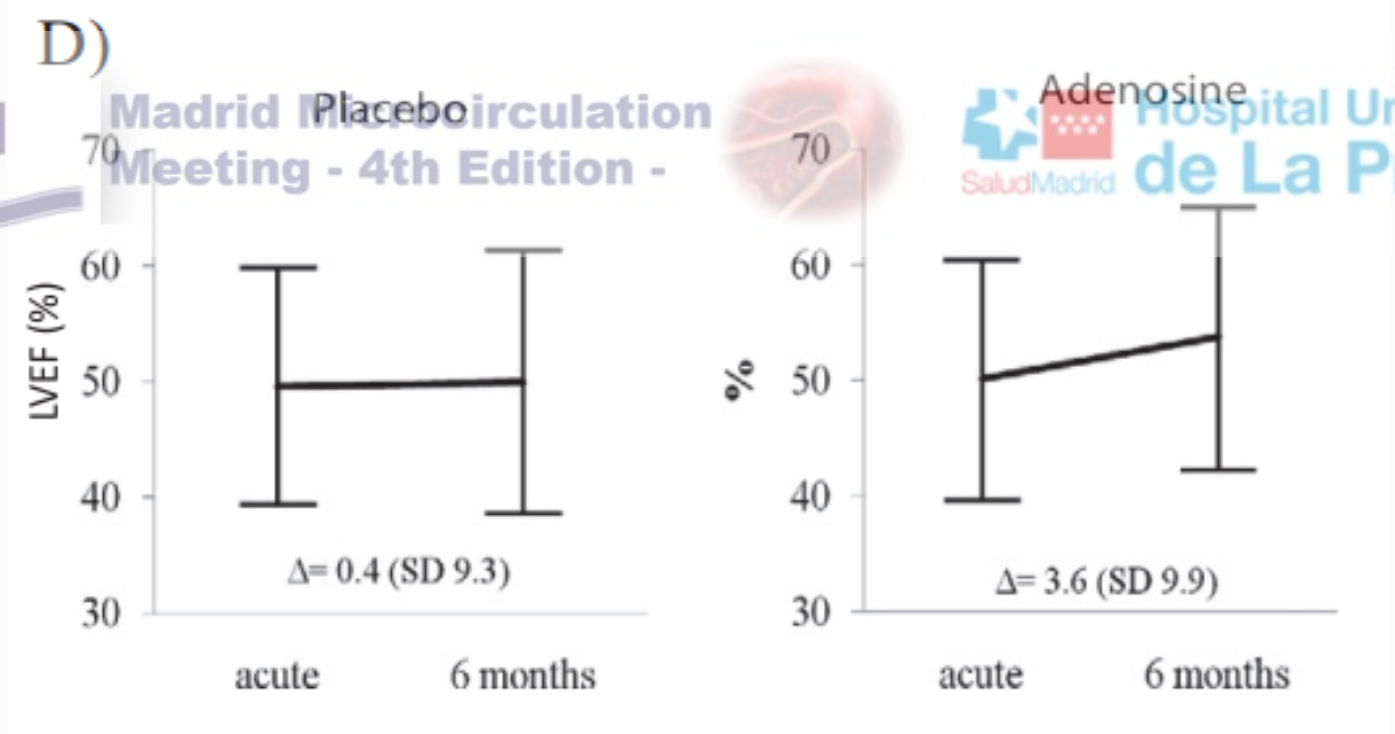
EF recovery



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50.01% (SD 11.31) vs. 53.8% (SD 11.17) ; *p* for interaction 0.06

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PROMISE trial. Adverse events

Table S1. Adverse outcomes judged as potentially related with the Adenosine

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	Placebo (n=97)	Adenosine (n=100)
Bradyarrhythmia (transient complete AV block)	4 (0)	2 (2)
Cutaneous erythema	1	0
Hypotension without bradyarrhythmia	0	1
Slow coronary flow after stent implantation	3	0
Heart failure during hospitalization	4	2
Ventricular arrhythmia during procedure	1	2
Atrial fibrillation during procedure (improbable)	1	0

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RESEARCH ARTICLE
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CC

Capillary pericytes mediate coronary no-reflow after myocardial ischaemia

Fergus M O'Farrell†, Svetlana Mastitskaya†, Matthew Hammond-Haley†, Felipe Freitas, Wen Rui Wah, David Attwell*

Department of Neuroscience, Physiology and Pharmacology, University College London, London, United Kingdom

Perycites

Pericytes contract in circumferential and longitudinal directions influencing the diameter and stiffness of capillaries

The close proximity of pericytes to sympathetic axons suggests that their tone may be under noradrenergic regulation

Pericytes have an established role in autoregulation of cerebral blood flow and contribute to vasoconstriction of cerebral capillaries and entrapment of erythrocytes and leukocytes in no-reflow zones following cerebral ischemia

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Pericyte

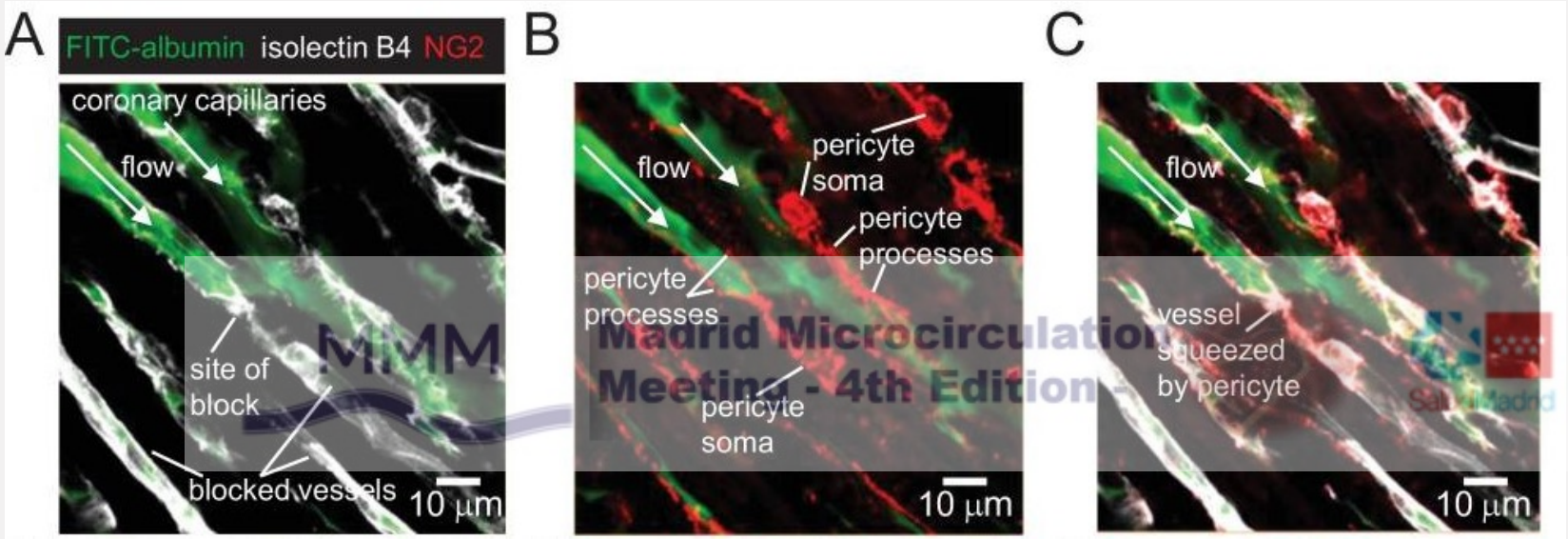

Figure 3.

No-reflow reflects blockage by pericyte constriction.

(**A**) Image of perfused and non-perfused capillaries in post-ischaemic left ventricle. Isolectin B_4 labelling (white) defines positions of all vessels, while FITC-albumin labelling (green) shows vessels that are perfused. Bottom left capillary is completely non-perfused; top green capillary is fully perfused; lower green capillary is blocked halfway across the image. (**B, C**): NG2-labelling of pericytes (**B**) and merge (**C**) of the images (**A**) and (**B**) show pericyte processes constricting vessel at block site.

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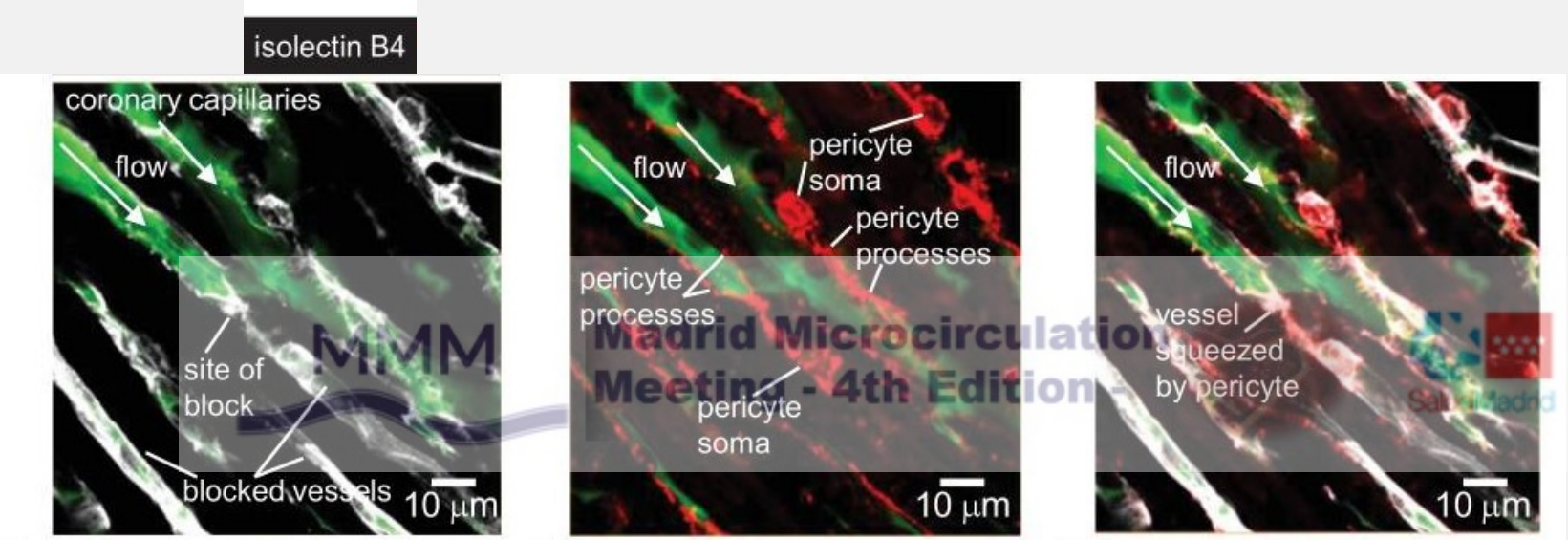
Fergus M O'Farrell, Svetlana Mastitskaya, Matthew Hammond-Haley, Felipe Freitas, Wen Rui Wah, David Attwell (2017) Capillary pericytes mediate coronary no-reflow after myocardial ischaemia eLife 6:e29280

Pericyte



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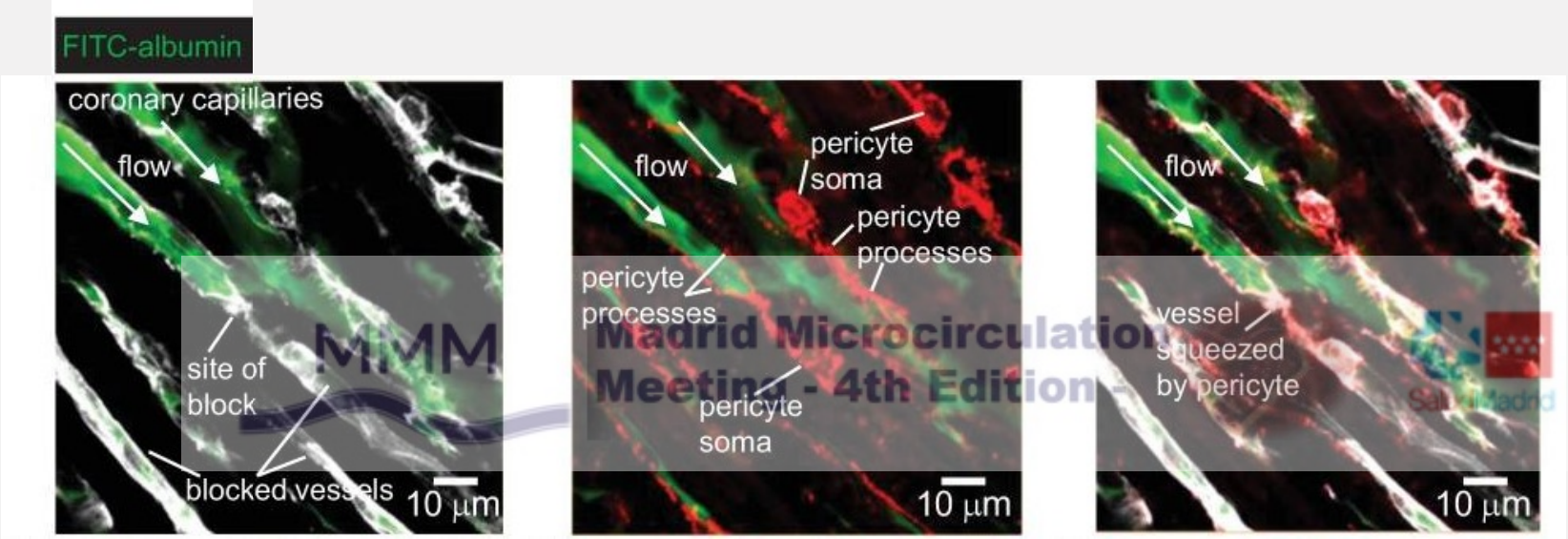

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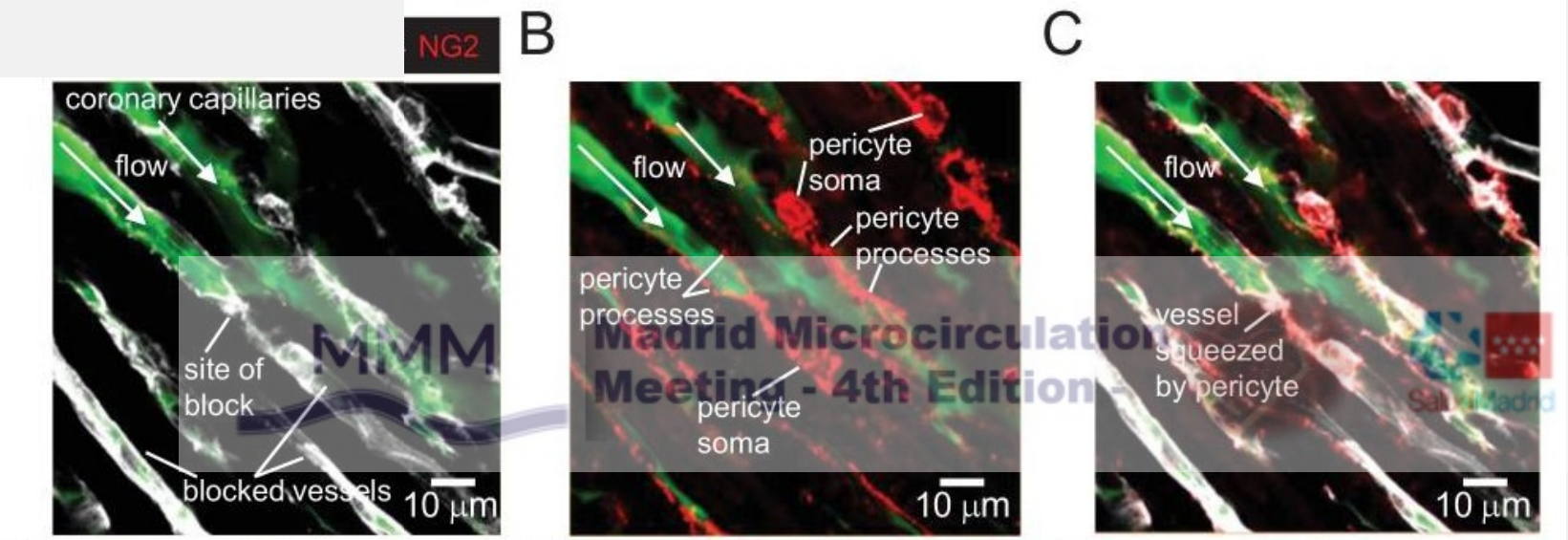

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Intravenous adenosine—a pericyte relaxant drug—increased the capillary diameter by 21% (at pericyte somata), decreased the capillary block by 25% and increased the perfusion volume by 57%

Adenosine also reduced by one quarter the percentage of capillaries that were blocked after reperfusion, from ~40% to ~30%

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THE END

Reperfusion-related injury

The most consistent histologic finding was demonstration of areas of swollen endothelium and formation of intraluminal membrane-bound protrusions or blebs that obstructed the capillary lumen

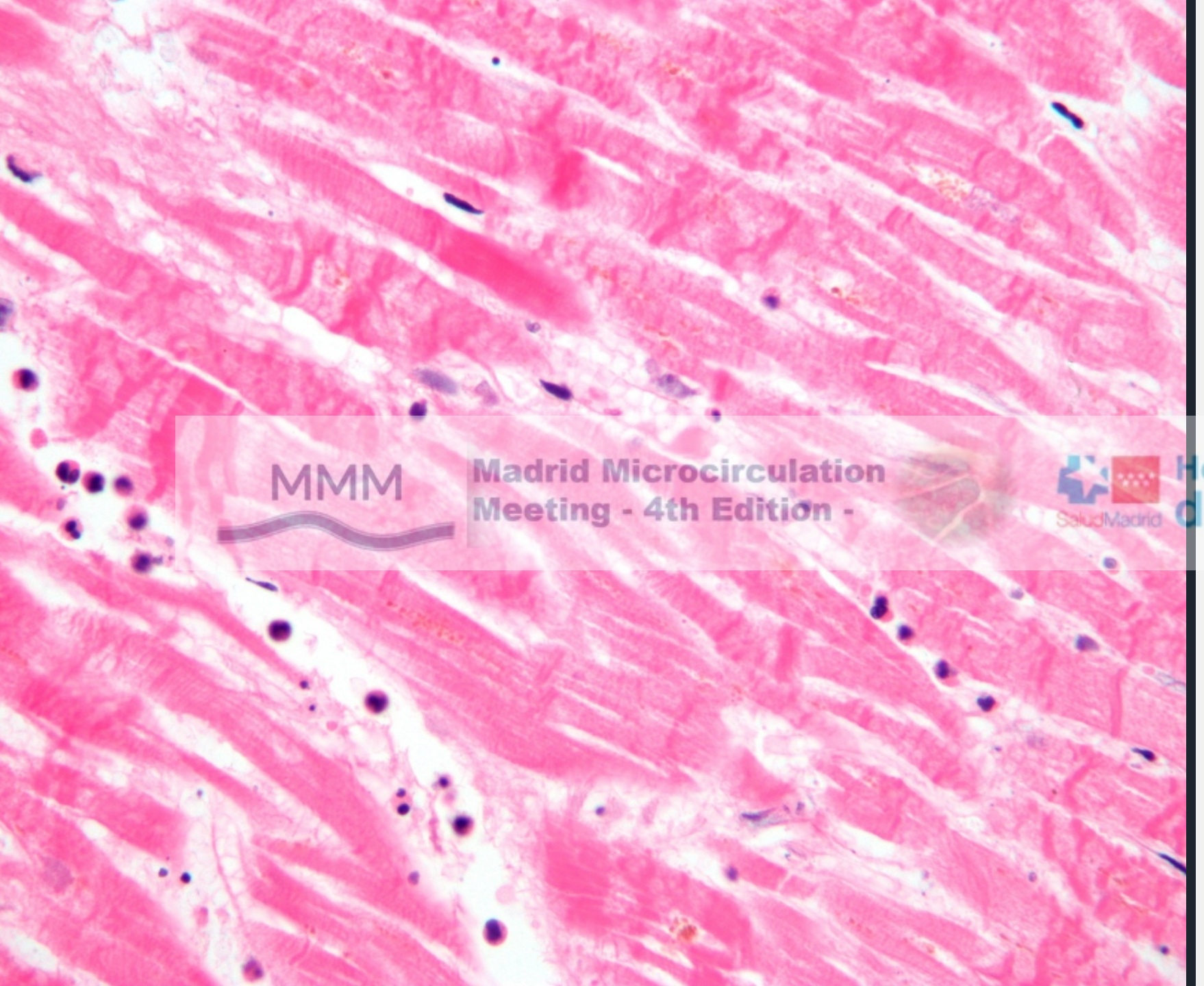
The local edema involving endothelium and surrounding myocardium suggested an initial restoration of some blood flow, which was later interrupted by reperfusion-induced MVO and swollen cardiomyocytes

Reperfusion-related injury

Upon restoration of blood flow, the extracellular pH is rapidly restored, which stimulates the Na+/H+ exchanger and Na+/HCO3- symporter leading to proton extrusion from the cells, rapid normalization of intracellular pH, massive Na^+ influx, and intracellular Ca^{2+} overload

The increased Ca^{2+} in endothelial cells leads to cellular retraction and intercellular gap formation and blebbing resulting in increased vascular permeability and obstruction of intracapillary space.

In addition to cellular swelling, increased ATP availability upon restoration of blood flow, restored intracellular pH and abundant cytoplasmic Ca^{2+} favor the hypercontracture of cardiomyocytes and contraction band formation—a histological marker of reperfusion



Contraction bands

High magnification micrograph showing contraction band necrosis and karyolysis. H&E stain

By Nephron - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=7507271

Myocardial ischemia

Platelet and leucocyte aggregates

Following activation by ischemia, platelets expose their adhesion molecules and aggregate to endothelial cells (facilitated by glycocalyx shedding), neutrophils, erythrocytes and to each other contributing to microcirculation obstruction

activated platelets release various biological active substances that contribute to proteolytic destruction of endothelial cells and intercellular junctions (and increased permeability), intracapillary blood coagulation, chemiotaxis and recruitment of leukocytes in microcirculation and promote inflammation, apoptosis and angiogenesis

Myocardial ischemia

Platelet and leucocyte aggregates

Neutrophils are recruited early in the ischemic myocardium

Neutrophils transmigrate through endothelial cells by interaction with endothelial cell junction proteins due to the highly chemotactic milieu in the ischemic microcirculation

Activated neutrophils aggregate with other cells and form neutrophil extracellular traps (NETs) clogging the microcirculation and impeding blood flow

Neutrophils are a major source of ROS, myeloperoxidase and proteolytic enzymes (such as, elastase and metalloproteinase-9), which in turn, promote degradation of all components of capillary barrier

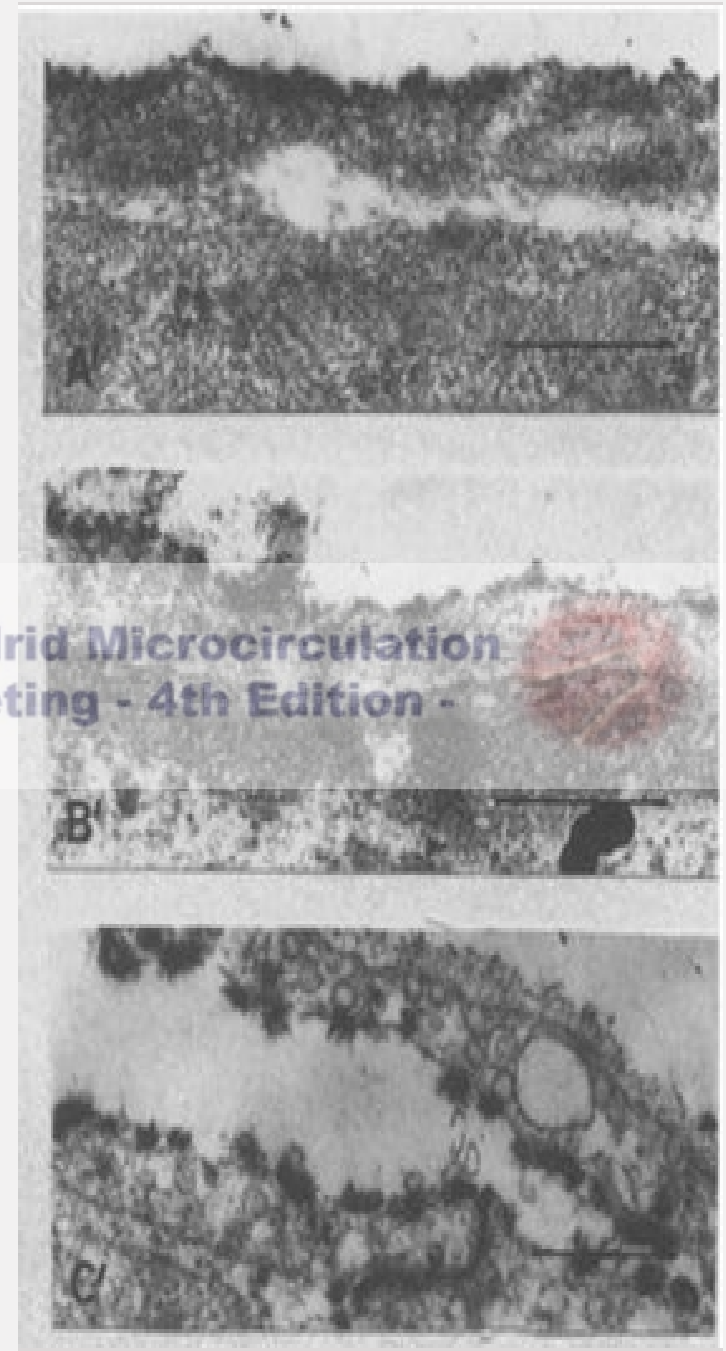
Myocardial ischemia

Glycocalyx damage

The thickness of glycocalyx exceeds the length of extracellular domains of most endothelial adhesion molecules, which in normal conditions prevents the adhesion of circulating cells to endothelial cells

The highly hydrophilic nature of glycocalyx enables creation of a relatively fixed water layer on the surface of endothelial cells, which together with electrostatic interactions with circulating erythrocytes, reduces the capillary hematocrit compared with that found in the systemic circulation and facilitates the passage of blood through the capillaries

Glycocalyx damage



Electron micrographs of left ventricular capillaries from isolated rat heart. Endothelial glycocalyx delineated with lanthanum chloride

A,A' Hearts perfused aerobically for 50 min;

B,B', 20 rain ischaemia;

C, C' 20 min ischaemia/3 min reperfusion

Czarnowska E, Karwatowska-Prokopczuk E. Ultrastructural demonstration of endothelial glycocalyx disruption in the reperfused rat heart. Involvement of oxygen free radicals. Basic Res Cardiol. 1995 Sep-Oct;90(5):357-64. doi: 10.1007/BF00788496. PMID: 8585856.

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Distal embolization

Angiographically visible distal embolization is documented in 5% to 17% of primary PCI procedures in patients with STEMI

However, the true incidence of lesser degrees of distal embolization appears to be much higher, with one study showing visible debris in 73% of patients who received a distal embolization protection system

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Distal embolization

Distal embolization is more frequent in atherosclerotic plaques with large volumes (particularly plaques with large necrotic core) and those with more thrombus at the lesion site

Erythrocyte-rich thrombi, larger culprit vessel, pre-balloon dilation and right coronary artery as culprit lesion have been identified as independently associated with a higher risk of distal embolization during the primary PCI procedures

Distal embolization

Since microthrombi preferentially end in well reperfused and viable myocardium (directed by blood stream), distal embolization kills potentially salvageable myocardium

One experimental study in dogs suggested that embolizing particles tend to flow away from the central infarcted area (forced by developing CNR) and accumulate in the infarct border contributing to infarct extension

Reperfusion related injury

Experimental studies in dogs by Kloner et al. (1974)

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JCI The Journal of Clinical Investigation

The "No-Reflow" Phenomenon after Temporary Coronary Occlusion in the Dog

Robert A. Kloner, … , Charles E. Ganote, Robert B. Jennings

J Clin Invest. 1974;54(6):1496-1508. https://doi.org/10.1172/JCI107898.

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Reperfusion-related injury

Since the areas of no reflow were often hyperemic and hemorrhagic and had capillaries which were packed with red blood cells, some flow must had occurred into these regions, probably during the first few seconds of reperfusion.

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