Fundació La Marató de TV3
21st SYMPOSIUM
Heart diseases

INTRAVENOUS ADMINISTRATION OF A MODIFIED HMG-COA REDUCTASE INHIBITOR AS A PROMISING CARDIOPROTECTIVE STRATEGY IN ISCHEMIC HEART DISEASE: UNRAVELLING THE CARDIOPROTECTIVE BENEFITS AND MECHANISMS OF ACTION IN A PRE-CLINICAL ANIMAL MODEL WITH HIGH TRANSLATABILITY

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1. Summary of the project

Ischemic heart disease remains the leading cause of death and disability worldwide. Timely reperfusion is the most effective strategy to reduce mortality. Yet, mortality still remains high and the development of heart failure due to large infarcts is increasing. Despite the efforts to generate successful therapeutic strategies aimed to attenuate myocardial infarction (MI)-related cardiac injury there is an unmet need to minimize myocardial damage and reduce cardiac remodeling post-MI. Oral administration of HMG-CoA reductase inhibitors (HMG-CoA-RI), beyond their lipid-lowering effects, has suggested minimizing the harmful effects triggered upon coronary revascularization. However, several therapeutic issues regarding HMG-CoA-RI remain unknown. Particularly, considering that "door-to-balloon" time has improved (<1h) and oral HMG-CoA-RI peak plasma concentration occurs ≈1.5-2h. Therefore, the optimal timing and route of administration of HMG-CoA-RI in high-risk patients have yet to be determined. It remains to be addressed whether intravenous HMG-CoA-RI therapy confers cardioprotection when given early after the onset of ischemia. In addition, further work is needed to decipher the mechanisms behind HMG-CoA-RI-related cardioprotective actions. Thanks to the granting of this project by the Fundació de la Marató TV3 we have been able to show that a single administration of an intravenous formulation of atorvastatin confers cardioprotection (reduction of cardiac damage) when administered shortly after the onset of coronary ischemia and that these effects protect against adverse cardiac remodeling and reinfarction to a greater extent than when the statin is administered orally after infarction. These studies have been carried out in a preclinical model of hypercholesterolemia (the most common cardiovascular risk factor) through the use of state-of-the-art imaging technologies. In addition, we have deciphered the mechanisms and signaling pathways involved in this cardioprotective actions by implementing molecular and histological approaches. Our findings deserve to be investigated in the clinical scenario since they may advance pre-hospital care and treatment after the identification of acute myocardial infarction patients.

2. Results obtained

First, we analyzed in a porcine model of acute myocardial infarction if the intravenous administration of a statin after the onset of ischemia symptoms protects against

myocardial necrotic cell death under normo- and hyper-cholesterolemic conditions. For this purpose, animals were fed a regular diet or a diet rich in saturated fats (20% saturated fat, 2% cholesterol, 1% colic acid) for 10 days. Subsequently, myocardial ischemia was induced in all pigs by percutaneous balloon occlusion of the left anterior descending coronary artery for 90 minutes. After the first 15 minutes of ischemia (associated with electrocardiographic elevation of the ST segment), animals were randomly distributed to receive an intravenous administration of the modified statin (loading dose equivalent to 0.5mg/kg) or the same volume in physiological saline as the vehicle. Blood samples were drawn before ischemia induction (baseline) and after 30, 60 and 90 minutes of ischemia. The following 3 early markers of myocardial necrosis were analyzed: myoglobin, ischemia modified albumin and cardiac fatty acid binding protein. At a molecular level we determined in the ischemic myocardium different markers of cell death (apoptosis) and inflammation. Animals (both normo- and hyper-cholesterolemic pigs) that had been given statin showed a significant reduction of the three markers of necrotic damage as compared to the animals that had received vehicle. This reduction, evident after 30min of ischemia, persisted during the 90min of ischemia and was associated with a global reduction of 70% in myoglobin, 60% in cardiac fatty acid binding protein and 75% in ischemia modified albumin. Such decrease in markers of cardiac damage was accompanied by a significant reduction in apoptosis-related markers (p53 and truncated caspase-3) and in the inflammatory response (lower MCP-1 expression). **In this first study we have shown that the early administration of a new intravenous statin formulation after complete coronary ischemia prevents ischemia-related myocardial necrosis and is associated with lower cell death and an inflammatory response.**

Subsequently we wanted to analyze whether the cardioprotective effect derived from the intravenous administration of a single loading dose of statin during the course of ischemia exerts higher cardioprotective effects as compared to oral administration post-myocardial infarction. For this purpose, animals were fed a hypercholesterolemic diet for 10 days and after this period they were randomly distributed to the following three arms: 1) received an oral loading dose of statin (80mg) 2 hours after ischemia; 2) received the modified statin intravenously (0.5mg/kg) during ischemia; or 3) received vehicle intravenously during ischemia. After 90 minutes of ischemia, the coronary artery of all animals was reperfused and the animals were administered oral

statin (40 mg/day) with the hyperlipidemic diet for the following 42 days. Serial cardiac magnetic resonance imaging (CMR) studies were performed on day 3 (acute remodeling phase) and on day 42 (late remodeling phase) in order to determine anatomical and functional (global and regional) parameters. On day 3, animals that were administered statin intravenously during ischemia showed a 10% reduction in the size of the infarction compared to the other two groups and the resultant 50% increase in myocardial salvage. At day 42, all animals that had received statin (either intravenous or oral) showed a significant decrease in scar size compared to those that received vehicle; however, those that received intravenous statin showed an additional reduction in scar size of 24% as compared to those treated orally after infarction. Functional analyses revealed an improvement in cardiac contractility in those animals that received intravenous statin as well as an improved regional contractility versus the rest. These beneficial structural and functional effects were associated with a higher collagen content and activation of a key cardiac metabolism molecule (AMPK) in the forming scar, higher density of vessels in the peri-infarct region, and lower activation of circulating inflammatory cells. **In this second study we have shown that intravenous administration of a modified statin reduces cardiac damage and improves contractility of the heart to a greater extent than oral administration after infarction. This protective effect is associated with an improved cardiac remodeling, both structurally and functionally, and at the molecular level with higher new vessel formation, enhanced deposition of collagen in the scar, and activation of cardioprotective signaling pathways.**

Finally, we aimed to examine whether intravenous administration of the modified statin during ischemia and oral administration after revascularization for 40 days protects against damage from reinfarction. To address this goal, pigs were kept under the same regime of a high cholesterol diet for 10 days after which they were induced complete coronary ischemia for 90 minutes. At 15 minutes of ischemia, the animals were randomly distributed to receive an intravenous infusion of the modified statin (0.5mg/kg) or vehicle. After 90 minutes of ischemia, the balloon was deflated and the animals were allowed to recover. All animals received oral statin (40 mg/day) together with the hyperlipidemic diet for 40 days.

After 40 days, all animals underwent CMR to determine global and regional parameters. The day after, animals underwent a second infarction (coronary occlusion

of 90min of ischemia followed by reperfusion). Three days after reinfarction, a new study CMR analysis was performed. In line with the results of the previous objective, the CMR at day 3 revealed a marked reduction in the size of infarction in those animals administered the statin intravenously as compared to the animals that received a vehicle. This effect persisted up to day 40. The most interesting finding was that induction of a second infarction did not expand the size of the scar in those animals that received the intravenous statin whereas, on the contrary, it increased by 13% the size of the scar in the animals that were orally administered the statin. These improvements in heart damage resulted in better global and regional contractility and fewer dysfunctional cardiac segments. At the molecular level, the scar of intravenous statin-treated reinfarcted animals showed lower cell death (apoptosis), a reduction in the expression of inflammatory markers and a greater vascular density compared to those that had received oral statin post-infarction. **In this third study we have proven that intravenous administration of statin during ischemia not only limits the damage due to infarction and improves ventricular remodeling to a greater extent than oral post-infarction administration but also protects against the deleterious effects derived of suffering reinfarction (lower cardiac necrosis, inflammatory response and improvement of global and regional cardiac function).**

3. Relevance and potential future implications

After the completion of the three objectives proposed in the context of dyslipidemia and acute myocardial infarction, we have demonstrated for the first time that intravenous administration of a modified form of an HMG-CoA reductase inhibitor (statin) early after suffering an ischemic coronary event reduces cardiac damage due to ischemia, favors the left ventricular remodeling process, improves cardiac contractility, and lessens the detrimental effects of reinfarction. These data hold great promise in the setting of acute myocardial infarction and cardioprotection.

Undoubtedly, our findings evidence the benefits that can be achieved from intravenously administering a single dose of statin during the onset of ischemia symptoms (e.g. during the ambulance transfer to the hospital) in patients suffering from myocardial infarction. After confirmation in the clinical setting, implementation of

our findings may lead to a significant improvement at a social-health-economic level since it will lead to a decline in morbidity and mortality due to coronary ischemic heart disease and heart failure as well as improving patient's quality of life.

4. Generated scientific bibliography

Publications

Mendieta G, Ben-Aicha S, Casani L, Badimon L, Sabaté M, Vilahur G.
Intravenous statin administration during ischemia exerts cardioprotective effects.
Journal of the American College of Cardiology July 2019;74(3):475-477.
Impact factor: 18.639
Q1 (D1)
Open access

Mendieta G, Ben-Aicha S, Casani L, Badimon L, Sabate M, Vilahur G.
Molecular pathways involved in the cardioprotective effects of intravenous statin administration during ischemia.
Basic Res Cardiol Nov 2019;115(1):2.
Impact factor: 6.470
Q1
Open access

Mendieta G, Ben-Aicha S, Manuel Gutierrez, Casani L, Aržanauskaitė M, Carreras F, Sabate M, Badimon L Vilahur G.
Intravenous statin administration during MI enhances cardioprotection compared to oral administration post-MI
Journal of the American College of Cardiology February 2020 (in press)
Impact factor: 18.639
Q1 (D1)
Open access

Meeting/Congress Communications

Mendieta G, Gutiérrez M, Casani L, Sabaté M, Badimon L, Vilahur G.
Reducción de la lesión isquémica miocárdica mediante la administración intravenosa precoz de cardioshield tras la elevación del segmento ST.
Oral presentation.
Congreso de las enfermedades cardiovasculares SEC 2016, Zaragoza

Mendieta G, Ben-Aicha S, Casani L, Badimon L, Sabate M, Vilahur G.
Treating ischemic injury to reduce infarct size and achieve cardiac protection.
Moderated Poster
Acute Cardiovascular Care Association 2019, Malaga

Mendieta G, Ben-Aicha S, Gutiérrez M, Casani L, Aržanauskaitė M, Carreras F, Sabate M, Badimon L, Vilahur G.
L'administració intravenosa d'estatina durant l'iam ofereix major cardioprotecció que atorvastatina via oral: estudi traslacional amb ressonància magnètica cardíaca.
Oral presentation.
XXXI Congrès de la Societat Catalana de Cardiologia 2019, Barcelona

Mendieta G, Ben-Aicha S, Gutiérrez M, Casani L, Aržanauskaitė M, Carreras F, Sabate M, Badimon L, Vilahur G.
Intravenous administration of IV-STATIN CARDIOSHIELD during myocardial infarction renders higher cardioprotection than oral atorvastatin given shortly after reperfusion: a translational CMR study.
Oral presentation.
European Society of Cardiology (ESC) Meeting 2019, Paris

This work was awarded with the "Young Investigator Award in Thrombosis of the European Society of Thrombosis" (First prize)

Vilahur G, Ben-Aicha S, Gutierrez M, Aržanauskaitė M, Mendieta G, Arderiu G, Casani L, Badimon L.
Intravenous administration of atorvastatin early after cardiac ischemia attenuates adverse left ventricular remodeling, ameliorates cardiac function and limits the deleterious effects of reinfarction.
Moderated Poster. European Society of Cardiology (ESC) Meeting 2019, Paris

Lecture – Invited Speaker

Speaker: Gemma Vilahur

Opportunities and challenges in translating cardioprotection to the clinic

Council of Basic Cardiovascular Science Summer Course; Heart House of the European Society of Cardiology

June 2017, Nice, France,

Speaker: Gemma Vilahur

Cardioprotection: where do we stand in 2018.

University of Oxford; Seminar at: department of physiology and genetics

February 2018, Oxford, United Kingdom,

Speaker: Gemma Vilahur

Nuevas dianas terapéuticas en cardioprotección

Xerencia de Xestión Integrada de Santiago de Compostela – Cardiochus. Servicio de Cardiología y UCC Area Cardiovascular

March 2019, Santiago Compostela, Spain

Speaker: Gemma Vilahur

Metabolic control of ischemia/reperfusion injury

American Heart Association

November 2019, Philadelphia, USA

Speaker: Gemma Vilahur

Novel Targets and Therapeutic Strategies that Bring New Hopes in Cardioprotection

Semmelweiss Symposium

November 2019, Budapest, Hungary

Speaker: Gemma Vilahur

Nuevas estrategias destinadas a favorecer la cardioprotección tras un infarto limitar la progresión hacia la insuficiencia cardíaca

Centro de Investigación de Medicina Aplicada (Clínica Universitaria de Navarra)

February 2020, Pamplona, Spain

Speaker: Gemma Vilahur

New therapeutic approaches to treat ischemic injury

COST – cardioprotection

March 2020

Riga, Latvia