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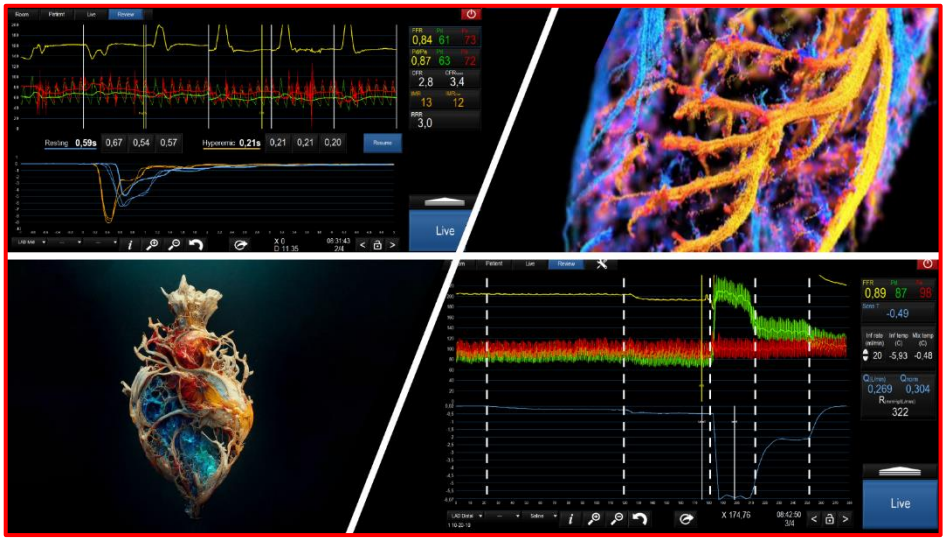

A comprehensive assessment of the coronary circulation: redefinition of physiological approaches and exploration of clinical settings

PhD thesis

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A comprehensive assessment of the coronary circulation: redefinition of physiological approaches and exploration of clinical settings

PhD Thesis

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"Valiente”

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CHAPTER 1

General introduction and outline of the thesis

Invasive coronary angiography has been uniformly accepted as the gold standard for assessing the presence of coronary artery disease (CAD) by defining its extension and guiding revascularization [(1)]. However considering the severity of stenosis reported as percentage of minimal lumen diameter, an intrinsic limitation based on the nature of 2-dimensional images affect the estimation of them. Because of this, correct visual evaluation is often not standardized and influenced by inter and intra operator variability, especially for intermediate stenosis (30-80%) or in challenging anatomies (tortuosity, diffuse CAD, branch overlap or eccentric/calcified lesion). Nowadays, in the "precision medicine" era, clinical decision making based only on a visual estimation affected by not negligible share of variability is inconceivable, even more in uncertain clinical scenario with asymptomatic patients or in absence of non-invasive ischemia test. However, the introduction of fractional flow reserve (FFR) has overcome the previous limitations by making the assessment reproducible and standardized, adding variables such as stenotic segment dependent myocardial mass and microvascular function that angiography alone cannot account for. The ability of FFR in ischemia detection were proved with randomized trial that shown the clear prognostic benefit in terms of death and MACCE of an FFR-guided PCI compared with the angiography-guided approach (FAME II, DEFER).

The rising of interest around coronary physiology beyond epicardial evaluation, starts from procedural and clinical observation. Failure of

coronary flow reserve (CFR) increase after PCI together with clinical scenario of angina or ischemia in patients with normal coronary artery, helps the researcher to clarify that our ability investigation involved only the 50% of the coronary circulation, the epicardial vessels. The microvascular compartment represented the missing part of the equation able to explain both phenomena and the study of which, expands the indications of coronary physiology assessment. However, by definition, CFR express the flow status in both epicardial and micro circulation and theoretically it might be influenced from the resting hemodynamics condition. The new index called IMR (index microcirculatory resistance) developed form Fearon WF et colleagues, is specific for the microvasculature and is independent from the hemodynamic variability, providing information about the vascular resistance without requiring additional equipment due to the possibility of a simultaneous measurement using the same pressure wire for FFR evaluation. However, during IMR assessment an intrinsic variability of resting mean transit time (Tmn_{rest}) of 7-10%, and Tmn_{hyp} of 4-8% have been reported. Bearing this in mind, an operators independent microcirculation assessment was achieved with the discovery of the continuous thermodilution method through a dedicated monorail catheter (Rayflow™, Hexacath, Paris, France), able to measure absolute coronary flow (Q) and microvascular resistance (R) in the cathlab. This technology based on saline hyperemia mechanism is completely operator independent and demonstrated higher reproducibility.

In this thesis we report the comparison of the two different thermodilution-based method (bolus vs thermodilution) in the context of angina with non-obstructive coronary disease (ANOCA) and the application of this technology in different clinical settings. The aim of the following study is to

describe how in less than 5 minutes with a single catheter using saline infusion, is possible to investigate the entire coronary circulation and collect fundamental information with clinical and prognostic impact.

Outline of the thesis

The thesis is divided in three parts:

Part I. Evolution of FFR from the "oldest" adenosine to the new saline continuous thermodilution: physiological mechanism and long-term prognostic impact. The first part of the thesis is dedicated to our research projects published, confirming the long-term prognostic impact of the deferral revascularization in patients with low ejection fraction. Furthermore, we investigate the physiological explanation behind the hyperemia induced by intracoronary saline administration and the following application in continuous thermodilution assessment. The main thread of this paragraph wants to underline how starting from the FFR, the coronary physiology gain relevance in the last years, developing new technology capable to explore the coronary circulation in both epicardial and microvascular beds with relevant clinical and prognostic impact.

Part II. New perspective in thermodilution-based Coronary Physiology: evaluation of different technique. In the second part of the thesis, we focused our research on the application of the last technology available in the field of coronary physiology assessment in ANOCA/INOCA patients. In particular we compared two different methods (Bolus vs Absolute flow), analyzing pros and cons of each assessment and underlining the impact of measurement's variability in the diagnosis of CMD.

Part III. Pattern characterization and prognostic values of a comprehensive coronary circulation assessment: when and how. In the third part of the thesis, we report the cluster of research projects that focuses on the application of the full physiology coronary assessment in different clinical settings providing the adding value of FFR, coronary flow reserve and microvascular resistance in terms of clinical pattern. In details we describe the pattern of microvascular disfunction in patients with HFrEF vs HEpEF and also in patients with diabetes, assessing the principals epicardial and microvascular indices. Furthermore, we evaluate coronary flow and microvascular resistance in patients with aortic stenosis before and after TAVI describing their variability and providing the physiological mechanism behind it. As part of the management of CAD, we also published an updated proposal algorithm to stratify the risk of coronary disease in order to guide the clinical decision-making process across the countless invasive and non-invasive method for CAD assessment. Lastly, we investigate the application of coronary flow evaluation in a case of "Slow Flow phenomena" discovering that this "angiographic definition" doesn't match with the effective CFR who is unexpecting normal/high.

Part IV. Other Lines of Research. We report in these sections other lines of research concerning aortic stenosis, myocardial biopsies and pharmacological treatment of diabetes with SGLT2i focusing on the prognostic impact of they after ACS. These projects, outside of the main subject of this thesis, deserve the same importance of the previous one because led with the same dedication and equal efforts of all the people involved.

Part I

Evolution of FFR from the “oldest” adenosine to the new saline continuous thermodilution: physiologycal mechanism and long-term prognostic impact

CHAPTER 2

Deferral of Coronary Revascularization in Patients with Reduced Ejection Fraction Based on Physiological Assessment: Impact on Long-Term Survival

The present study sought to establish the long term prognostic value of FFR-guiding versus angiography-guided PCI stratified by left ventricular function in intermediate coronary stenosis using a propensity score matching analysis.

Background: Deferring revascularization in patients with nonsignificant stenoses based on fractional flow reserve (FFR) is associated with favorable clinical outcomes up to 15 years. Whether this holds true in patients with reduced left ventricular ejection fraction is unclear. We aimed to investigate whether FFR provides adjunctive clinical benefit compared with coronary angiography in deferring revascularization of patients with intermediate coronary stenoses and reduced left ventricular ejection fraction.

Methods: Consecutive patients with reduced left ventricular ejection fraction (≤50%) undergoing coronary angiography between 2002 and 2010 were screened. We included patients with at least 1 intermediate coronary stenosis (diameter stenosis ≥40%) in whom revascularization was deferred based either on angiography plus FFR (FFR guided) or angiography alone (angiography guided). The primary end point was the cumulative incidence of all-cause death at 10 years. The secondary end point (incidence of major adverse cardiovascular and cerebrovascular events) was a composite of all-cause death, myocardial infarction, any revascularization, and stroke.

Results: A total of 840 patients were included (206 in the FFR-guided group and 634 in the angiography-guided group). Median follow-up was 7 years (interquartile range, 3.22–11.08 years). After 1:1 propensity-score matching, baseline characteristics between the 2 groups were similar. All-cause death was significantly lower in the FFR-guided group compared with the angiography-guided group (94 [45.6%] versus 119 [57.8%]; hazard ratio [HR], 0.65 [95% CI, 0.49–0.85]; P<0.01). The rate of major adverse cardiovascular and cerebrovascular events was lower in the FFR-guided group (123 [59.7%] versus 139 [67.5%]; HR, 0.75 [95% CI, 0.59–0.95];P=0.02) (Figure 2 and 3).

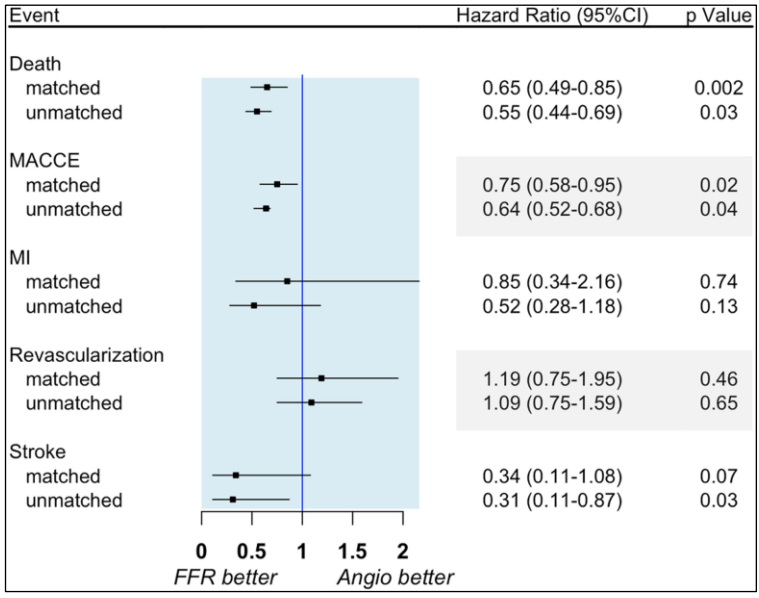

Figure 1: Clinical end points after deferring revascularization in the matched and unmatched populations. Angio indicates angiography; FFR, fractional flow reserve; MACCE, major adverse cardiovascular and cerebrovascular event; and MI, myocardial infarction.

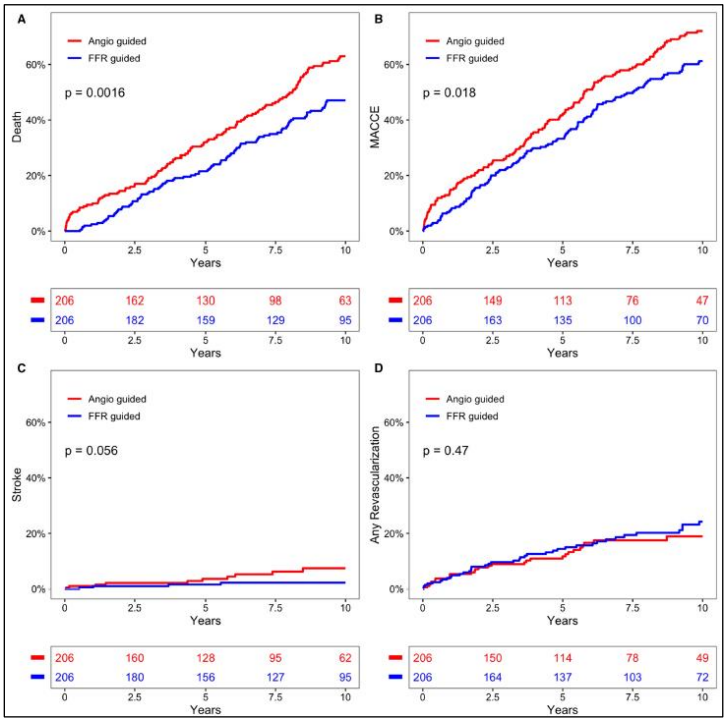

Figure 4: Kaplan-Meier event curves for clinical outcomes in the matched cohort. All-cause death (A); major adverse cardiovascular and cerebrovascular events (MACCEs) (B); stroke (C); and any revascularization (D). Angio indicates angiography; and FFR, fractional flow reserve.

The impact of deferring revascularization based on FFR was assessed as continuum of LVEF. Interestingly, when an FFR-guided strategy was compared with an angiography-guided strategy by using LVEF as continuous variable, the FFR-guided group showed lower probability of death, especially for LVEF higher (Figure 4), whereas for lower values, the impact of an FFR-based strategy seemed to be neglectable. This was supported by the regression analysis performed in the LVEF subgroups (≥45%, 35%–45%, and <35%). An FFR-based strategy of deferral revascularization was shown to be a predictor of lower probability.

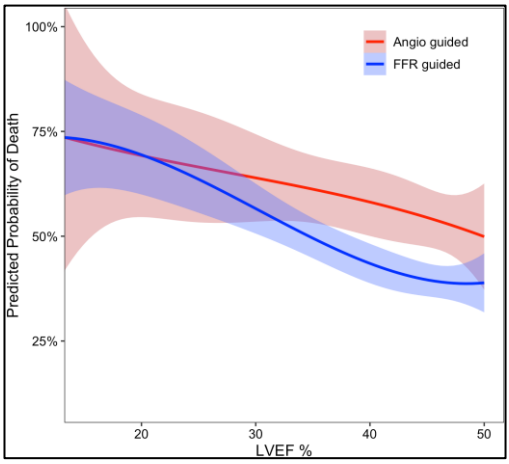

Figure 4: Predicted probability of death per group in the matched cohort, according to the left ventricular ejection fraction (LVEF), presented as a continuous variable. Angio indicates angiography; and FFR, fractional flow reserve.

Conclusions: In patients with reduced left ventricular ejection fraction, deferring revascularization of intermediate coronary stenoses based on FFR is associated with a lower incidence of death and major adverse cardiovascular and cerebrovascular events at 10 years.

CHAPTER 3

Saline-induced coronary hyperemia with continuous intracoronary thermodilution is mediated by intravascular hemolysis

Background and Aims: Absolute coronary flow can be measured by intracoronary continuous thermodilution of saline through a dedicated infusion catheter (RayFlow®). A saline infusion rate at 15–20 mL/min induces an immediate, steady-state, maximal microvascular vasodilation. The mechanism of this hyperemic response remains unclear. We aimed to test whether local hemolysis is a potential mechanism of saline-induced coronary hyperemia.

Methods: Absolute coronary flow can be measured by intracoronary continuous thermodilution of saline through a dedicated infusion catheter (RayFlow®). A saline infusion rate at 15–20 mL/min induces an immediate, steady-state, maximal microvascular vasodilation. The mechanism of this hyperemic response remains unclear. We aimed to test whether local hemolysis is a potential mechanism of saline-induced coronary hyperemia (Figure 5).

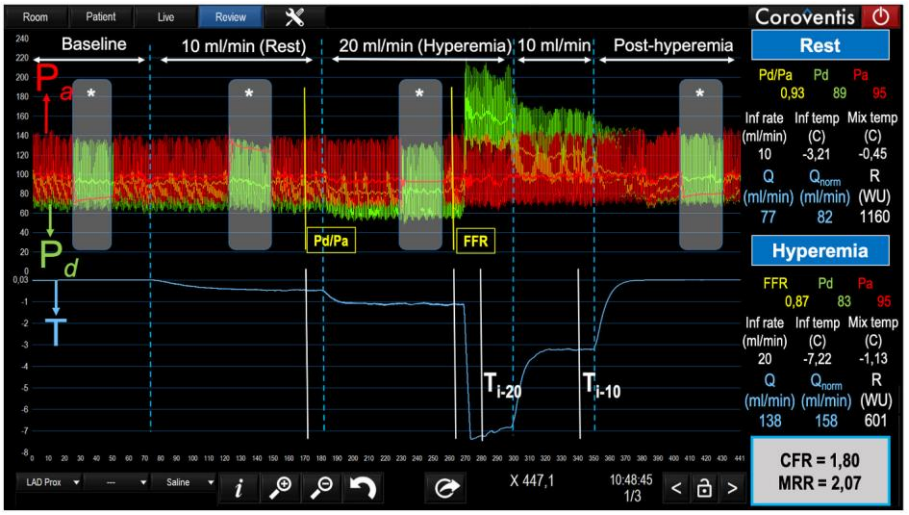

Figure 5: Sequence of pressure and temperature measurements in the study. Simultaneous recording of Pd, Pa and temperature in the coronary artery. During each step of the study, blood samples were recorded as shown by the temporary interruption of the Pa signal (*). At baseline, the temperature recorded is 0 ◦C; then, saline is infused through the RayFlow catheter at 10 ml/min for resting flow assessment, and the temperature recorded by the wire located in the distal part of the coronary artery starts decreasing (Mix temp). Thereafter, the infusion rate is increased via the pump to 20 mL/min, thus inducing hyperemia and a further decrease in the distal coronary temperature. Then the wire is pulled back, and the pressure/temperature sensor is placed at the tip of the Rayflow catheter in order to measure the temperature of the saline infused at 20 mL/min (Ti). Next, the infusion rate is lowered again via the pump to 10 mL/min, to record the infusion temperature of the saline at 10 mL/min (Ti10). Finally, saline infusion is stopped, and the temperature returns to 0 ◦C (post-hyperemia phase).

Results: Hemolysis was visually detected only in the centrifugated venous blood samples collected during the Hyperemia phase. As compared to Rest, during Hyperemia both LDH (131.50 ± 21.89 U/dL [Rest] and 258.33 ± 57.40 U/dL [Hyperemia], $p < 0.001$) and plasma free hemoglobin (PFHb, 4.92 ± 3.82 mg/dL [Rest] and 108.42 ± 46.58 mg/dL [Hyperemia], $p < 0.001$) significantly increased in the coronary sinus. The percentage of hemolysis was significantly higher during the Hyperemia phase (0.04 ± 0.02% [Rest] vs 0.89 ± 0.34% [Hyperemia], $p < 0.001$) (Figure 6).

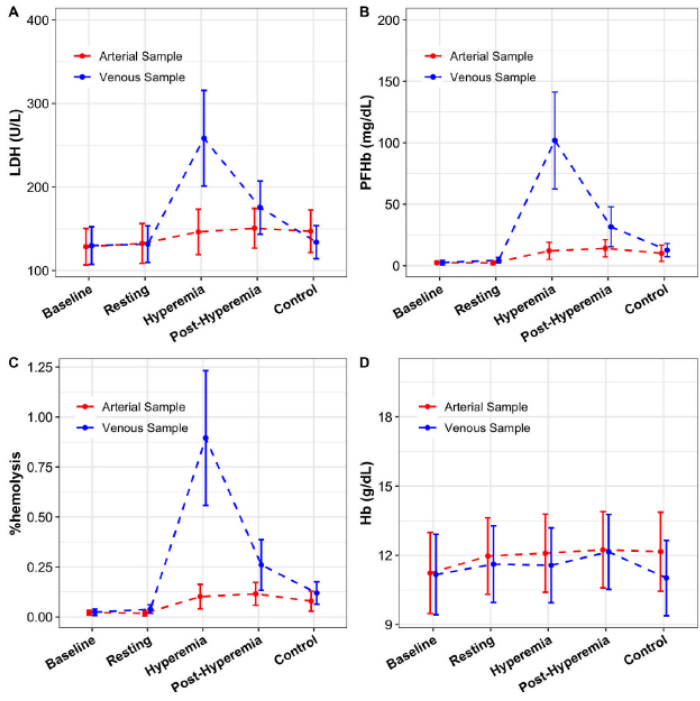

Figure 6: Distribution of the analyte values across different phases of the study. Line plot with error bars showing the values of the main analytes measured during each phase of the protocol. Red lines represent the arterial samples, blue lines the venous samples. A) LDH, B) PFHb, C) % of Hemolysis, D) Hb. LDH, lactate dehydrogenase; PFHb, plasma free hemoglobin; Hb, hemoglobin.

Conclusions: Saline-induced hyperemia through a dedicated intracoronary infusion catheter is associated with hemolysis. Vasodilatory compounds released locally, like ATP, are likely ultimately responsible for localized microvascular vasodilatation.

Part II

New perspective in thermodilution-based coronary physiology: evaluation of different technique.

CHAPTER 4

Reproducibility of bolus versus continuous thermodilution for assessment of coronary microvascular function in patients with ANOCA

Background: A bolus thermodilution-derived index of microcirculatory resistance (IMR) has emerged as the standard for assessing coronary microvascular dysfunction (CMD). Continuous thermodilution has recently been introduced as a tool to quantify absolute coronary flow and microvascular resistance directly. Microvascular resistance reserve (MRR) derived from continuous thermodilution has been proposed as a novel metric of microvascular function, which is independent of epicardial stenoses and myocardial mass.

Aims: This study was designed to assess the reproducibility of bolus and continuous thermodilution in assessing coronary microvascular function.

Methods: Patients with angina and non-obstructive coronary artery disease (ANOCA) at angiography were prospectively enrolled. Bolus and continuous intracoronary thermodilution measurements were obtained in duplicate in the left anterior descending artery (LAD). Patients were randomly assigned in a 1:1 ratio to undergo either bolus thermodilution first or continuous thermodilution first.

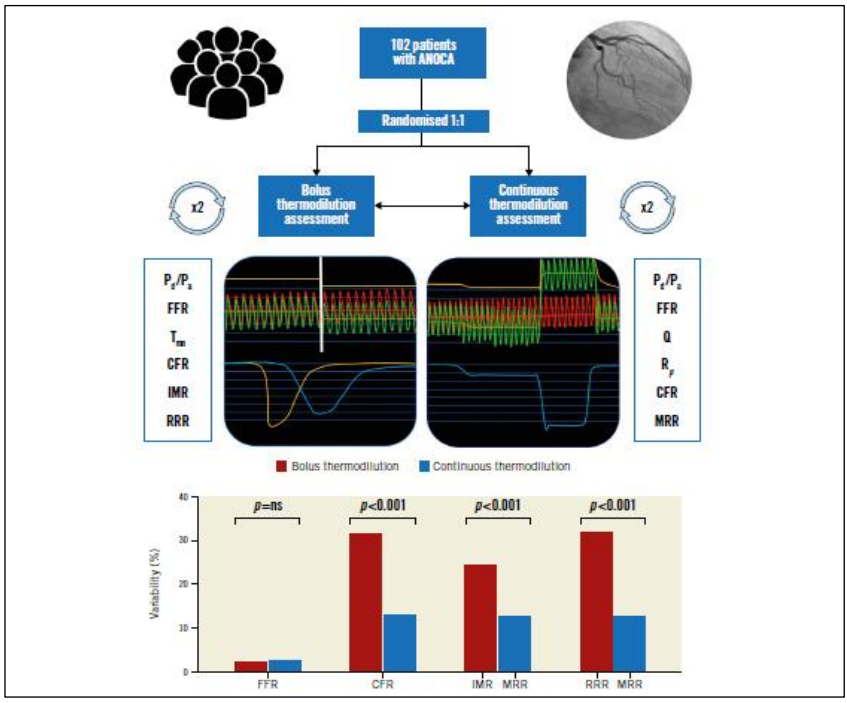

Figure 7. Study Design and principals' results of the bolus vs continuous thermodilution. CFR: coronary flow reserve; FFR: fractional flow reserve; IMR: index of microvascular resistance; MRR: microvascular resistance reserve; ANOCA: angina and non-obstructive coronary artery; Pa: aortic pressure; Pd: distal coronary pressure; Q: absolute coronary blood flow; RRR: resistance reserve ratio; Rμ: absolute microvascular resistance; Tmn: mean transit time

Results: A total of 102 patients were enrolled. The mean fractional flow reserve (FFR) was 0.86±0.06. Coronary flow reserve (CFR) calculated with continuous thermodilution (CFR_{cont}) was significantly lower than bolus thermodilution-derived CFR (CFR_{bolus}; 2.63±0.65 vs 3.29±1.17; p<0.001). CFR_{cont} showed a higher reproducibility than CFR_{bolus} (variability: 12.7±10.4% continuous vs 31.26±24.85% bolus; p<0.001). MRR showed a higher reproducibility than IMR (variability 12.4±10.1% continuous vs 24.2±19.3% bolus; p<0.001) (Figure 7-8). No correlation was found between MRR and IMR (r=0.1, 95% confidence interval: −0.09 to 0.29; p=0.305) (Figure 7).

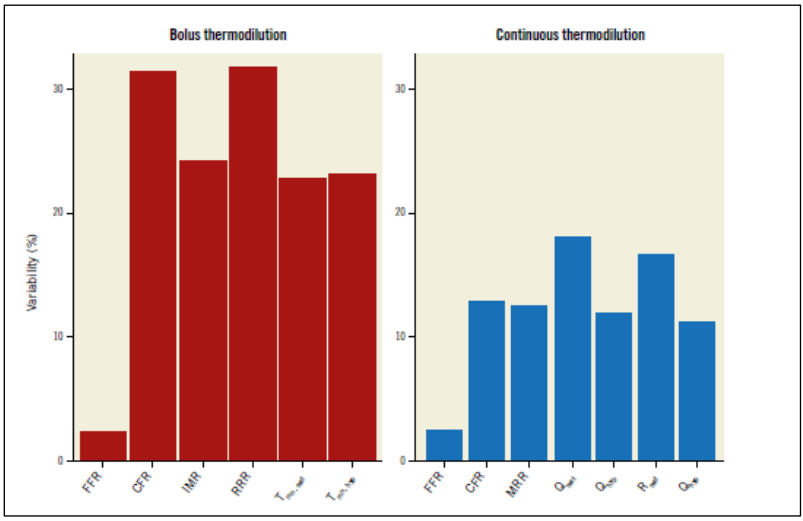

Figure 8. Variability of bolus thermodilution- and continuous thermodilution-derived measurements. Barplots with the variability (expressed as %) of the main indices derived by bolus and continuous thermodilution. CFR: coronary flow reserve; FFR: fractional flow reserve; IMR: index of microvascular resistance; MRR: microvascular resistance reserve; Qhyp: absolute hyperemic coronary flow; Qrest: absolute coronary flow at rest; RRR: resistance reserve ratio; Rμ,hyp: absolute resistance during hyperaemia; Rμ,rest: absolute resistance at rest; Tmn,hyp: mean transit time during hyperaemia; Tmn,rest: mean transit time at rest.

Conclusions: In the assessment of coronary microvascular function, continuous thermodilution demonstrated significantly less variability on repeated measurements than bolus thermodilution.

CHAPTER 5

Continuous vs Bolus Thermodilution to Assess Microvascular Resistance Reserve

Background: Coronary flow reserve (CFR) and microvascular resistance reserve (MRR) can, in principle, be derived by any method assessing coronary flow.

Aims: The aim of this study was to compare CFR and MRR as derived by continuous (CFR_{cont} and MRR_{cont}) and bolus thermodilution (CFR_{bolus} and MRR_{bolus}).

Methods: A total of 175 patients with chest pain and nonobstructive coronary artery disease were studied. Bolus and continuous thermodilution measurements were performed in the left anterior descending coronary artery. MRR was calculated as the ratio of CFR to fractional flow reserve and corrected for changes in systemic pressure. In 102 patients, bolus and continuous thermodilution measurements were performed in duplicate to assess test-retest reliability.

Results: Mean CFR_{bolus} was higher than CFR_{cont} (3.47 ± 1.42 and 2.67 ± 0.81 [P < 0.001], mean difference 0.80, upper limit of agreement 3.92, lower limit of agreement -2.32)(Figure 9). Mean MRR_{bolus} was also higher than MRR_{cont} (4.40 ± 1.99 and 3.22 ± 1.02 [P < 0.001], mean difference 1.2, upper limit of agreement 5.08, lower limit of agreement -2.71) (Figure 10). The correlation between CFR and MRR values obtained using both methods was significant but weak (CFR, r = 0.28 [95% CI: 0.14-0.41]; MRR, r = 0.26 [95%

CI: 0.16-0.39]; P < 0.001 for both). The precision of both CFR and MRR was higher when assessed using continuous thermodilution compared with bolus thermodilution (repeatability coefficients of 0.89 and 2.79 for CFR_{cont} and CFR_{bolus}, respectively, and 1.01 and 3.05 for MRR_{cont} and MRR_{bolus}, respectively)

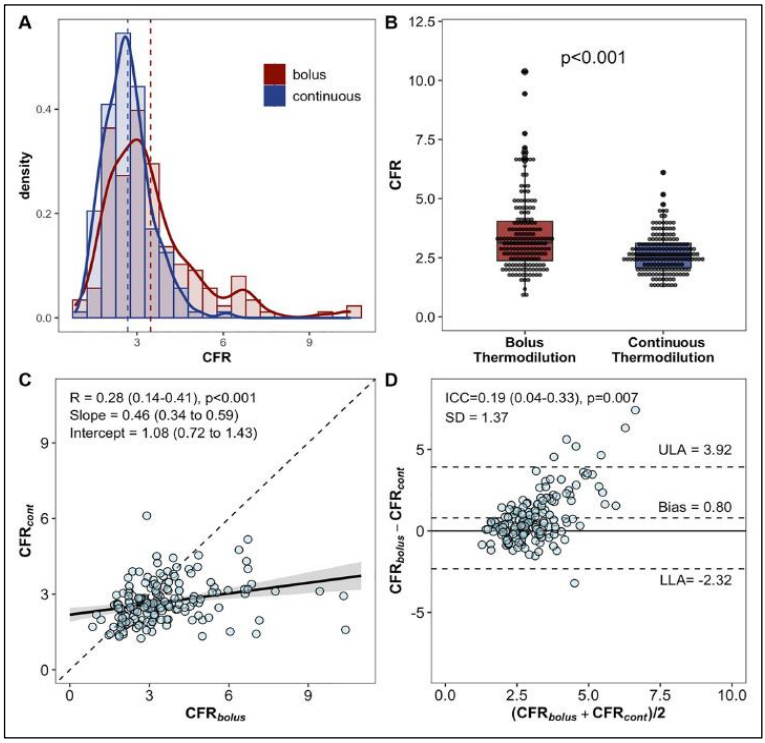

Figure 9: (A) Data distribution of coronary flow reserve (CFR) values derived using bolus (CFR_{bolus}) and continuous thermodilution (CFR_{cont}). **(B)** Box plot with comparison between CFRbolus and CFR_{cont}. Horizontal lines within the box represent the median values, and top and bottom edges of the boxes represent the 25% of values above and below the median value. (C, D) Correlation and Bland-Altman plot between CFR_{bolus} and CFR_{cont}. The straight line in (C) represents the correlation line, and the shadow represents the 95% CI. ICC = intraclass correlation coefficient; LLA = lower limit of agreement; ULA = upper limit of agreement.

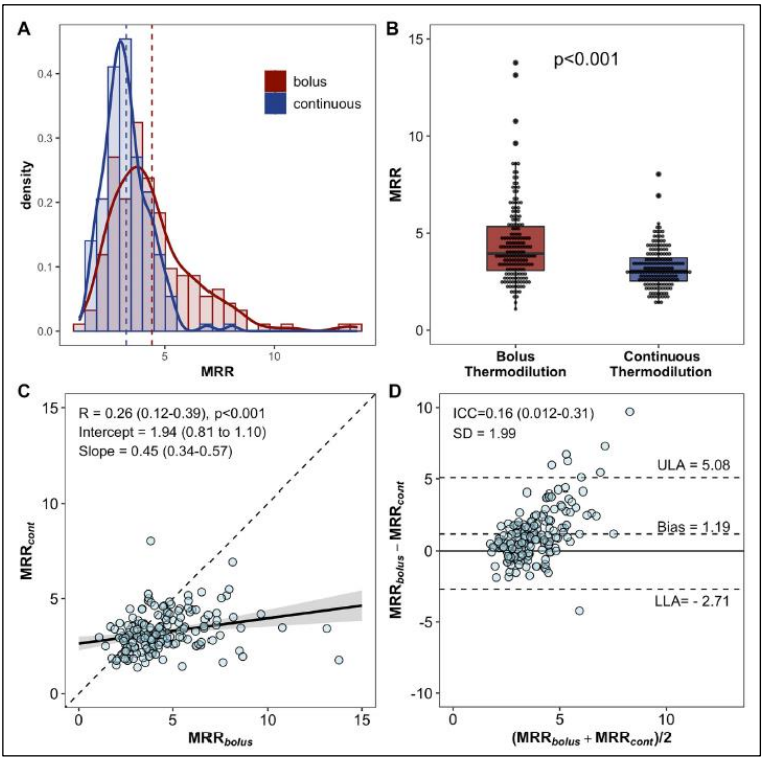

Figure 10: (A) Data distribution of MRR values derived using bolus and continuous thermodilution. **(B)** Box plot with comparison between MRR_{bolus} and MRR_{cont}. Horizontal lines within the box represent the median values, and top and bottom edges of the boxes represent the 25% of values above and below the median value. **(C, D)** Correlation and Bland-Altman plot between MRR_{bolus} and MRR_{cont}. The straight line in **(C)** represents the correlation line, and the shadow represents the 95% CI.

Conclusions: Compared with bolus thermodilution, continuous thermodilution yields lower values of CFR and MRR accompanied by an almost 3-fold reduction of the variability in the measured results.

Part III

Pattern characterization and prognostic values of a comprehensive coronary circulation assessment: when and how.

CHAPTER 6

FOCUS ON DIABETES

Microvascular Dysfunction in Patients with Type II Diabetes Mellitus: Invasive Assessment of Absolute Coronary Blood Flow and Microvascular Resistance Reserve.

Background: Coronary microvascular dysfunction (CMD) is an early feature of diabetic cardiomyopathy, which usually precedes the onset of diastolic and systolic dysfunction. Continuous intracoronary thermodilution allows an accurate and reproducible assessment of absolute coronary blood flow and microvascular resistance thus allowing the evaluation of coronary flow reserve (CFR) and Microvascular Resistance Reserve (MRR), a novel index specific for microvascular function, which is independent from the myocardial mass. In the present study we compared absolute coronary flow and resistance, CFR and MRR assessed by continuous intracoronary thermodilution in diabetic vs. non-diabetic patients. Left atrial reservoir strain (LASr), an early marker of diastolic dysfunction was compared between the two groups.

Methods: In this observational retrospective study, 108 patients with suspected angina and non-obstructive coronary artery disease (NOCAD) consecutively undergoing elective coronary angiography (CAG) from September 2018 to June 2021 were enrolled. The invasive functional assessment of microvascular function was performed in the left anterior descending artery (LAD) with intracoronary continuous thermodilution. Patients were classified according to the presence of DM. Absolute resting and hyperemic coronary blood flow (in mL/min) and resistance (in WU) were compared between the two cohorts. FFR was measured to assess coronary epicardial lesions, while CFR and MRR were calculated to assess microvascular function. LAS, assessed by speckle tracking echocardiography, was used to detect early myocardial structural changes potentially associated with microvascular dysfunction.

Results: The median FFR value was 0.83 [0.79–0.87] without any significant difference between the two groups. Absolute resting and hyperemic flow in the left anterior descending coronary were similar between diabetic and non-diabetic patients. Similarly, resting and hyperemic resistances did not change significantly between the two groups (Figure 11).

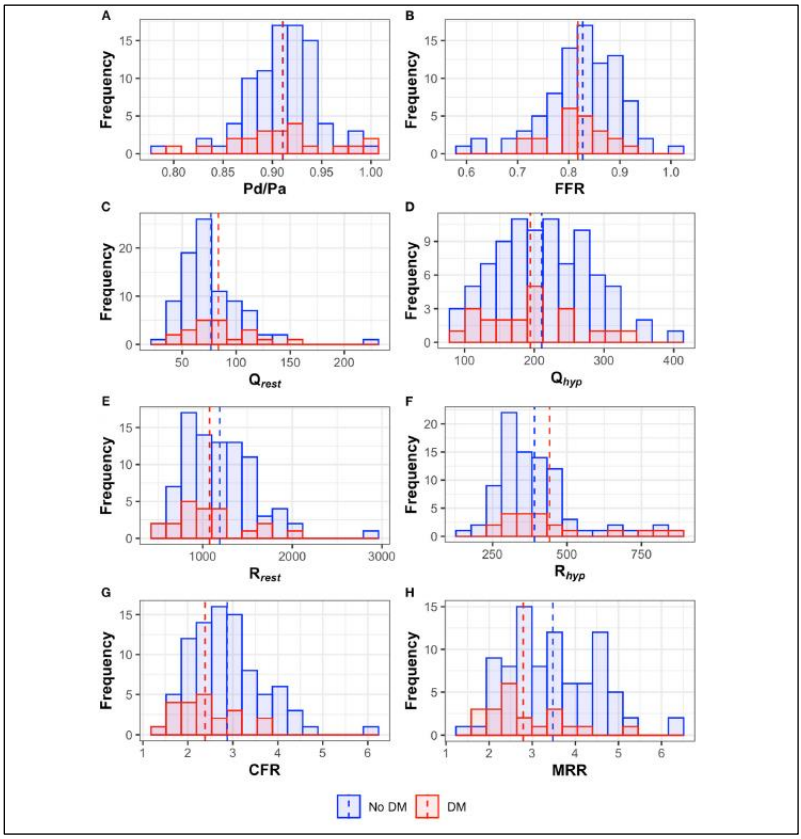

Figure 11. Histograms and median values (dotted line) of the hemodynamic parameters [(A) Pd/Pa, (B) fractional flow reserve – FFR, (C) resting flow, (D) hyperemic flow, (E) resting resistance, (F) hyperemic resistance, (G) coronary flow reserve – CFR, (H) microvascular resistance reserve – MRR] in both diabetic and non-diabetic patients.

In the DM cohort the CFR and MRR were significantly lower compared to the control group (CFR = 2.38 ± 0.61 and 2.88 ± 0.82; MRR = 2.79 ± 0.87 and 3.48 ± 1.02 for diabetic and non-diabetic patients respectively, [$p<0.05$ for both]) (Figure 12). Likewise, diabetic patients had a significantly lower reservoir, contractile and conductive LAS (all $p < 0.05$).

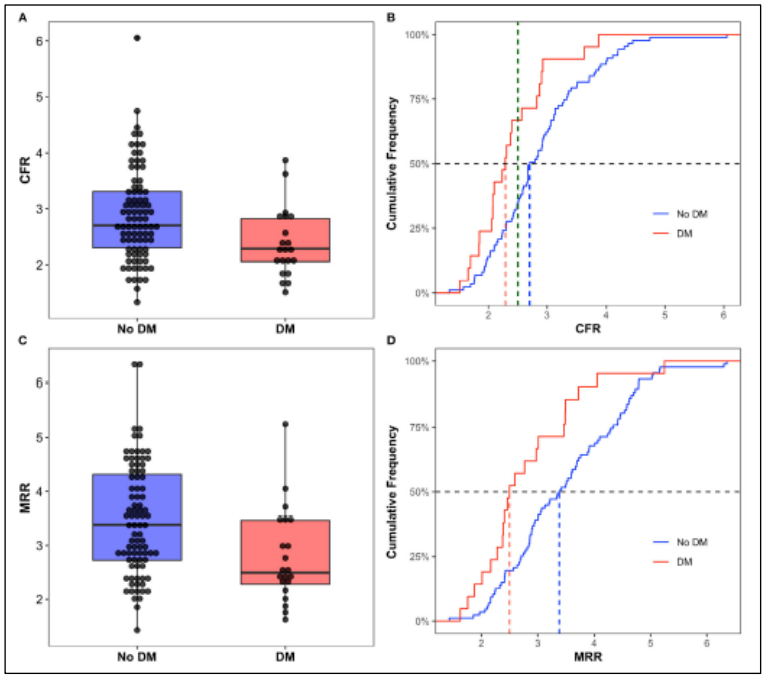

Figure 12. Box Plot and Cumulative Frequency of CFR (A,B) and MRR (C,D) in diabetic and non-diabetic patients. In the (B) the dashed green line corresponds to a CFR = 2.5. DM, Diabetes Mellitus; CFR, Coronary Flow Reserve; MRR, Microvascular resistance Reserve.

Conclusions: Compared with non-diabetic patients, CFR and MRR were lower in patients with DM and non-obstructive epicardial coronary arteries, while both resting and hyperemic coronary flow and resistance were similar. LASr was lower in diabetic patients, confirming the presence of a subclinical diastolic dysfunction associated to the microcirculatory impairment. Continuous intracoronary thermodilution-derived indexes provide a reliable and operator-independent assessment of coronary macro- and microvasculature and might potentially facilitate widespread clinical adoption of invasive physiologic assessment of suspected microvascular disease.

CHAPTER 7

FOCUS ON AORTIC STENOSIS

Absolute coronary flow and microvascular resistance reserve in patients with severe aortic stenosis

Background: Development of left ventricle (LV) hypertrophy in aortic stenosis (AS) is accompanied by adaptive coronary flow regulation. We aimed to assess absolute coronary flow, microvascular resistance, coronary flow reverse (CFR) and microvascular resistance reserve (MRR) in patients with and without AS.

Methods: Absolute coronary flow and microvascular resistance were measured by continuous thermodilution in 29 patients with AS and 29 controls, without AS, matched for age, gender, diabetes, and functional severity of epicardial coronary lesions. Myocardial work, total myocardial mass and left anterior descending artery (LAD)-specific mass were quantified by echocardiography and cardiac-CT.

Results: Patients with AS presented a significantly positive LV remodeling with lower global longitudinal strain and global work efficacy compared with controls. Total LV myocardial mass and LAD-specific myocardial mass was significantly higher in patients with AS ($p=0.001$). Compared with matched controls, absolute resting flow in the LAD was significantly higher in the AS cohort ($p=0.009$), resulting into lower CFR and MRR in the AS cohort compared with controls ($p<0.005$ for both). No differences were found in hyperemic flow and resting and hyperemic resistances (Figure 13).

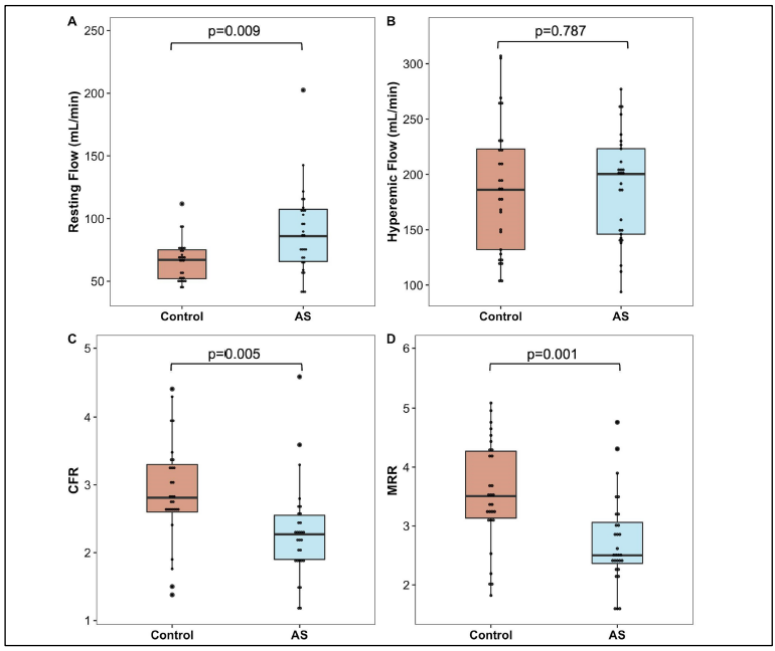

Figure 13. Panels A and B: comparison of the resting (rest Q) and hyperaemic flow (hyp Q) in patients with and without aortic stenosis; in the AS cohort, absolute resting flow was significantly higher (p=0.009) as compared with controls, while absolute hyperaemic flow was similar between the two study cohorts. Panel C and D: comparison of CFR and MRR in patients with and without aortic stenosis; both CFR and MRR were significantly lower in the AS cohort compared with controls (p=0.005 and p=0.001, respectively). CFR, coronary flow reserve; Hyp Q, hyperaemic flow; MRR, microvascular resistance reserve; Rest Q, resting flow.

Moreover, in our study, we found that the resting absolute flow—but not the hyperemic—is significantly increased in patients with AS, explaining the significant reduction of both CFR and MRR in this population. The rising in intraventricular pressures induced by the AS leads to LV hypertrophy to lower wall stress with the disadvantage to further increase myocardial oxygen demand. To balance these hemodynamic changes, coronary flow autoregulation induces vasodilation and minimize coronary microvascular resistance to maintain a constant resting perfusion. Since the hyperemic flow cannot further increase, the progressive reduction in CFR appears to be related to a proportional increase in resting coronary flow (Figure 14). Myocardial perfusion (assessed as blood flow per g of tissue subtended to the LAD − QN expressed in ml/min/g) during hyperemia was significantly

lower in patients with AS. Thus, with the progression of myocardial hypertrophy, the compensatory mechanism of increased resting flow maintains an adequate perfusion at rest, but not during hyperemia (Figure 14).

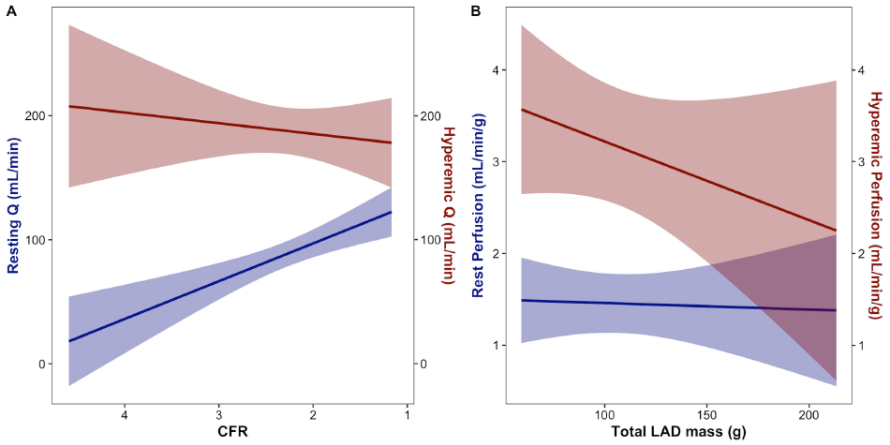

Figure 14. Panel A: Absolute flow variation in function of CFR in patients with AS. The hyperemic flow, represented by the red line, remains relatively constant despite the reduction in CFR whereas the resting flow (blue line) tends to increase as the CFR tends to lower values. Therefore, in patients with AS, the reduction in CFR is mainly the consequence of an increased resting flow. **Panel B:** Myocardial resting (blue line) and hyperemic (redline) perfusion expressed in flow per gram of tissue in the LAD. With the progression of LVH, the compensatory mechanism of increased resting flow maintains an adequate perfusion at rest, but not during hyperemia. CFR, coronary flow reserve; LAD, left anterior descending artery; LVH, left ventricle hypertrophy.

Conclusions: In patients with severe AS and non-obstructive coronary artery disease, with the progression of LV hypertrophy, the compensatory mechanism of increased resting flow maintains adequate perfusion at rest, but not during hyperemia. As a consequence, both CFR and MRR are significantly impaired.

Absolute coronary flow and microvascular resistance before and after transcatheter aortic valve implantation: The Absolute-TAVR Study

Background: Severe aortic stenosis (AS) is associated with left ventricular (LV) remodeling which is likely to lead to changes in coronary blood flow and microvascular resistance.

Aims: To evaluate changes in absolute coronary flow and microvascular resistance, in patients with AS undergoing transcatheter aortic valve replacement (TAVR).

Methods: Consecutive patients with AS undergoing TAVR were included if they had no obstructive coronary disease (DS>50%) in the left anterior descending artery (LAD). Absolute coronary flow and microvascular resistance were measured in the LAD by continuous intracoronary thermodilution at rest (Q_{rest} and $R\mu_{,rest}$) and during hyperaemia (Q_{hyp} and $R\mu_{,hyper}$) before and after TAVR, and at 6-month follow-up. Total myocardial mass and LAD-specific mass were quantified by echocardiography and cardiac-CT. Regional myocardial perfusion (Q_N) was calculated by dividing absolute flow for the subtended myocardial mass.

Results: In 51 patients absolute flow and microvascular resistance were measured at rest and during hyperemia before and after TAVR; in 20 (39%) patients, measurements were also obtained 6 months after TAVR. In the overall population, there were no changes in resting and hyperemic flow and resistance before and after TAVR. Similarly, there was no change in flow and resistance after 6 months (Figure 15). In patients with significant LV

reverse remodeling at follow-up led to an increase in hyperemic perfusion ($Q_{N,\ hyp}$: 0.86 [0.69-1.06] vs 1.20 [0.99-1.32] mL/min/g, p=0.008; pre-TAVR and follow-up respectively) but not in resting perfusion ($Q_{N,\ rest}$: 0.34 [0.30-0.48] vs 0.47 [0.36-0.67] mL/min/g, p=0.06).

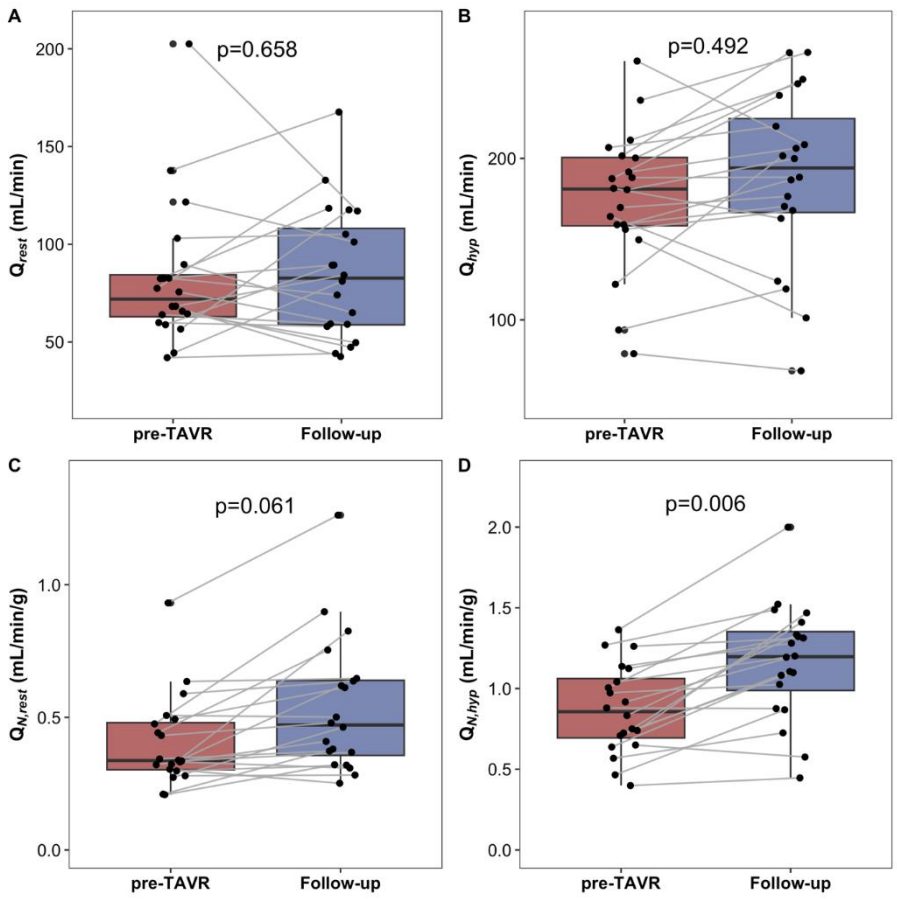

Figure 15: Boxplot with stripchart showing differences between absolute flow and myocardial perfusion at rest (Q_{rest} and $Q_{N\text{-}rest}$) and during hyperaemia (Q_{hyp}, $Q_{N,hyp}$) at baseline (pre-TAVR) and at follow-up.

In patients with significant LV reverse remodeling at follow-up led to an increase in hyperemic perfusion ($Q_{N,\ hyp}$: 0.86 [0.69-1.06] vs 1.20 [0.99-1.32] mL/min/g, p=0.008; pre-TAVR and follow-up respectively) but not in resting perfusion ($Q_{N,\ rest}$: 0.34 [0.30-0.48] vs 0.47 [0.36-0.67] mL/min/g, p=0.06) (Figure 16).

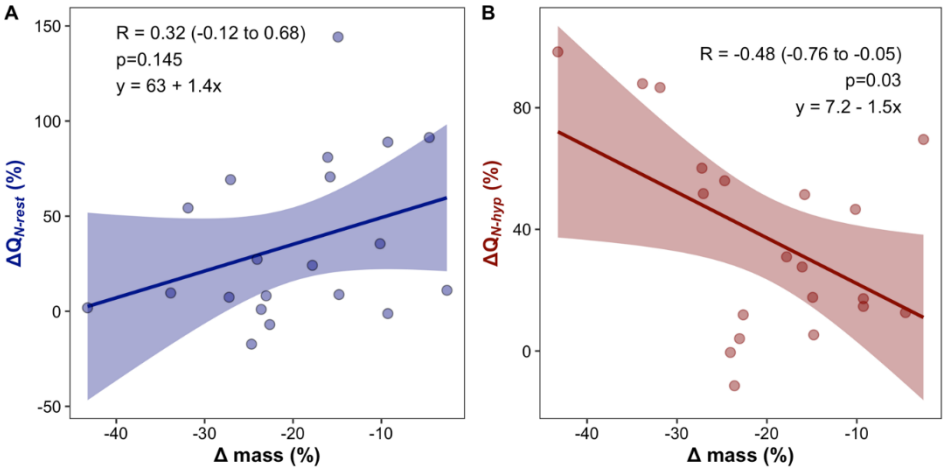

Figure 16: Scatter plot with correlation and regression equation between relative changes in perfusion and mass before TAVR and at follow up. ΔQ_N represent the relative change expressed as percentage between myocardial perfusion before and after TAVR (both at rest ($\Delta Q_{N\text{-}rest}$)and during hyperaemia ($\Delta Q_{N\text{-}hyp}$)). Δmass represent the relative changes in the subtended mass before TAVR and at follow-up expressed as percentage.

Conclusions: Immediately after TAVR no changes occurred in absolute coronary flow and coronary flow reserve. Over time, the remodeling of the left ventricle is associated with increased hyperemic perfusion.

CHAPTER 8

FOCUS ON HEART FAILURE

Coronary Microvascular Dysfunction in Patients With Heart Failure: Characterization of Patterns in HFrEF Versus HFpEF

Background: Coronary microvascular dysfunction (CMD) is involved in heart failure (HF) onset and/or progression, independently of HF phenotype and obstructive coronary artery disease (CAD). Invasive assessment of CMD might provide insights into phenotyping and prognosis of patients with HF.

Objectives. To assess absolute coronary flow (Q), microvascular resistance (R), perfusion (Q_N), coronary flow reverse (CFR) and microvascular resistance reserve (MRR) in HF patients with preserved (HFpEF) and with reduced (HFrEF) left ventricular ejection fraction.

Methods: Single-center, prospective study of 56 consecutive patients with de novo HF without obstructive CAD, divided into HFpEF (n=21) and HFrEF (N=35) groups. CMD was invasively assessed by intracoronary continuous thermodilution and defined as CFR<2.5. Left ventricular (LV) and left anterior descending artery (LAD)-related myocardial mass were quantified by echocardiography and coronary CT angiography.

Results: 51.8% of the study population had CMD, with a similar prevalence between the 2 groups. In HFrEF, CMD was characterized by lower R and higher Q at rest ("functional CMD"). In patients with HFpEF, CMD was mainly due to higher R and lower Q during hyperemia ("structural CMD")

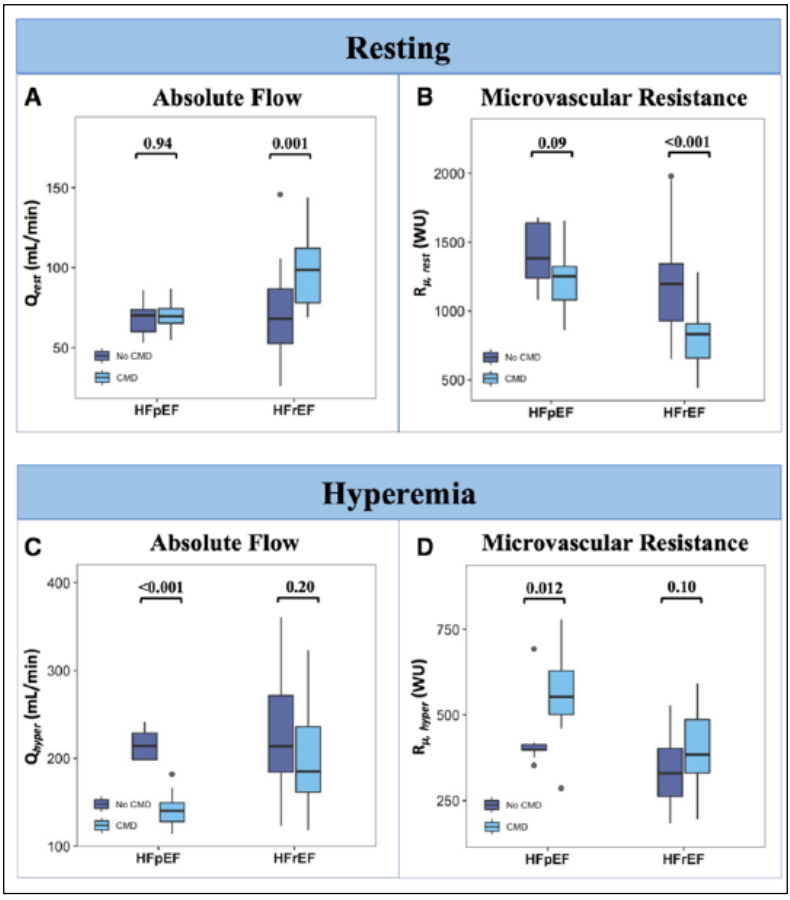

Figure 17: Comparison of flow and resistance in patients with both heart failure (HF) phenotypes, stratified according to the presence of coronary microvascular dysfunction (CMD).

The relationship between CFR and R were showed in Figure 18 in which HFrEF cohort is characterized of lower $R_{\mu\text{-rest}}$ and $R_{\mu\text{-hyper}}$ comparing with the

HFpEF (p<0.001 for both). Furthermore, HFrEF patients showed a significant LV remodeling with higher total LV and LAD-related myocardial mass, lower global longitudinal strain and global work efficacy compared to HFpEF (p<0.010 for all). CMD was an independent predictor of a lower rate of LV reverse remodeling at follow-up (Figure 18).

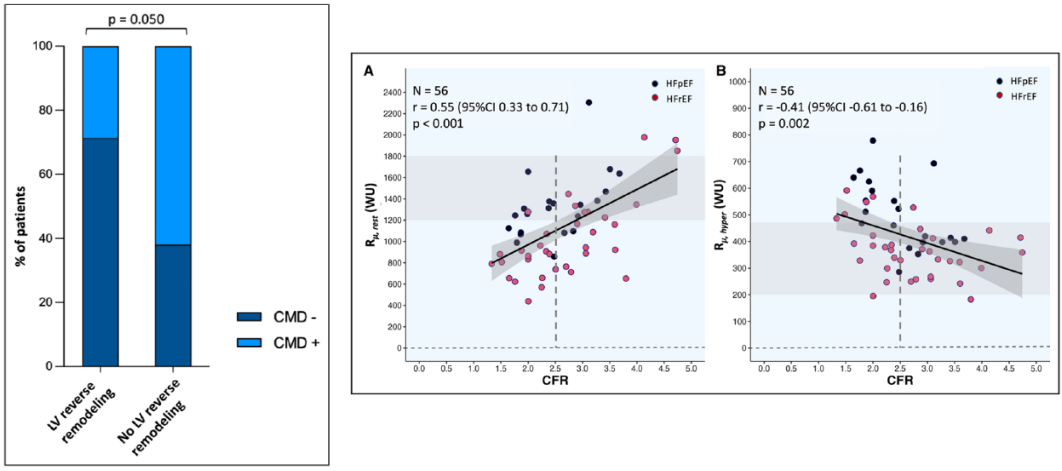

Figure 18: Proportion of patients with and without coronary microvascular dysfunction (CMD) among patients with heart failure with reduced ejection fraction, stratified by the presence of left ventricular (LV) reverse remodeling at follow-up (left panel). Correlation between coronary flow reserve (CFR; x-axis) and resting and hyperemic resistance (y-axis) in both heart failure (HF) phenotypes (right panel).

Conclusion: Continuous intracoronary thermodilution allows the definition and characterization of distinct CMD patterns in patients with HF and could identify HFrEF patients with a higher rate of LV reverse remodeling at follow-up.

CHAPTER 9

FOCUS ON SLOW FLOW

When "Slow Flow" Is Not "Low Flow"

Classically a delayed progression of contrast across a non-stenotic epicardial vessel during a coronary angiogram, is often defined to as "low" or "slow" flow phenomena—both terms being considered interchangeable—and is often ascribed to microvascular dysfunction. However, for a given value of absolute flow, flow velocity depends on the cross-sectional area of the vessel. Because of this, and based on the angiogram, we expect to find low CFR and higher IMR values using a bolus-based measurements with an agreement with the continuous thermodilution Q and R. When a 75 years old man was referred to our catheterization lab for control coronary angiogram 6 month after a primary PCI on the LCx, we found a TIMI frame count of 57 in the LAD with surprisingly physiology results (Figure 14).

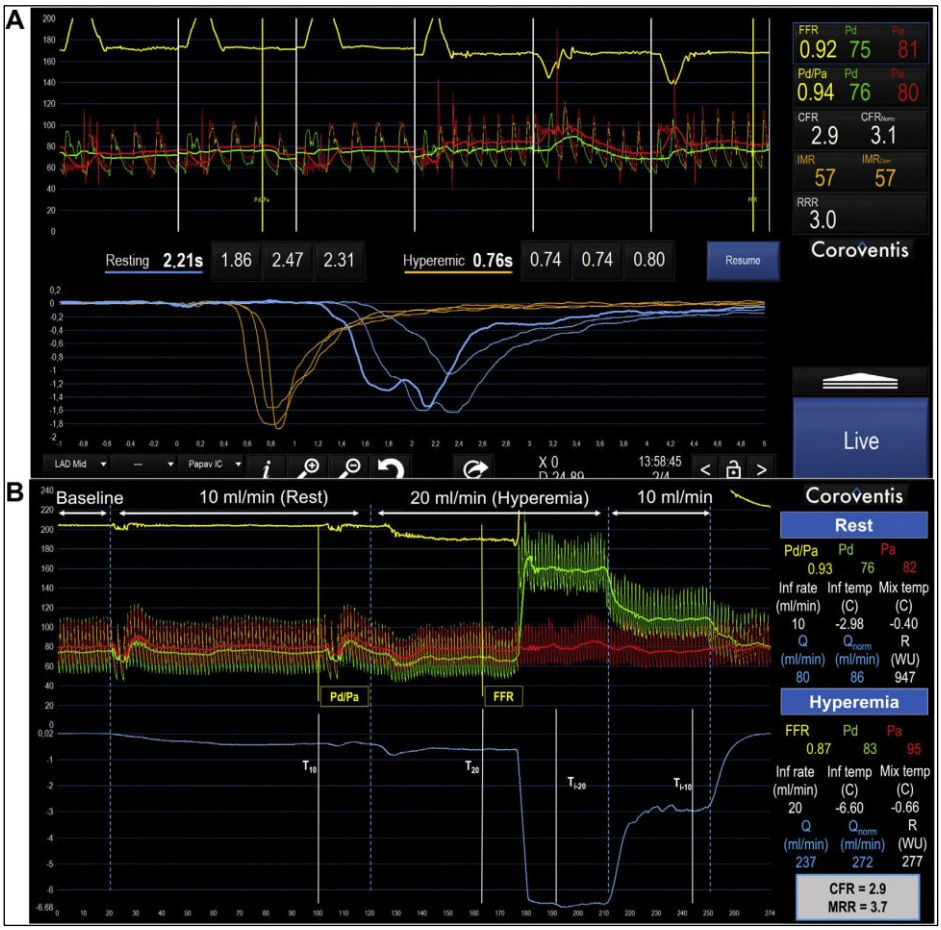

Figure 14: Complete physiological assessment of a patients with slow flow phenomena. A) Bolus thermodilution assessment. (B) Continuous thermodilution assessment.

Invasive assessment were performed, revealing normal coronary flow (CFR , Q rest and Q hyper) with both technique in contrast with the angiographic findings. Moreover, a mismatch between resistance were found, with higher IMR (bolus thermodilution) and normal values of R_{rest} and R_{hyper} (continuous thermodilution)[1]. This case example illustrates how “slow flow” does not necessarily correspond to “low flow” and high microvascular resistance. In such cases (ie, ectasic vessels) when IMR could be not reliable, absolute flow and resistance assessment may overcome this limitation.

CHAPTER 10

FOCUS ON STABLE CAD

Contemporary Management of Stable Coronary Artery Disease

Coronary artery disease (CAD) continues to be the leading cause of mortality and morbidity in developed countries. In this review we propose an updated diagnostic and therapeutic approach for the management of patients with CAD based on the latest invasive and non-invasive technologies available nowadays (Figure 15). Assessment of pre-test probability (PTP) based on patient's characteristics, gender and symptoms, help to identify more accurate patient's clinical likelihood of coronary artery disease. Consequently, non-invasive imaging tests are performed more appropriately to rule in or rule out CAD rather than invasive coronary angiography (ICA). Coronary computed tomography angiography (CCTA) is the first-line non-invasive imaging technique in patients with suspected CAD and could be used to plan and guide coronary intervention. Invasive coronary angiography remains the gold-standard method for the identification and characterization of coronary artery stenosis

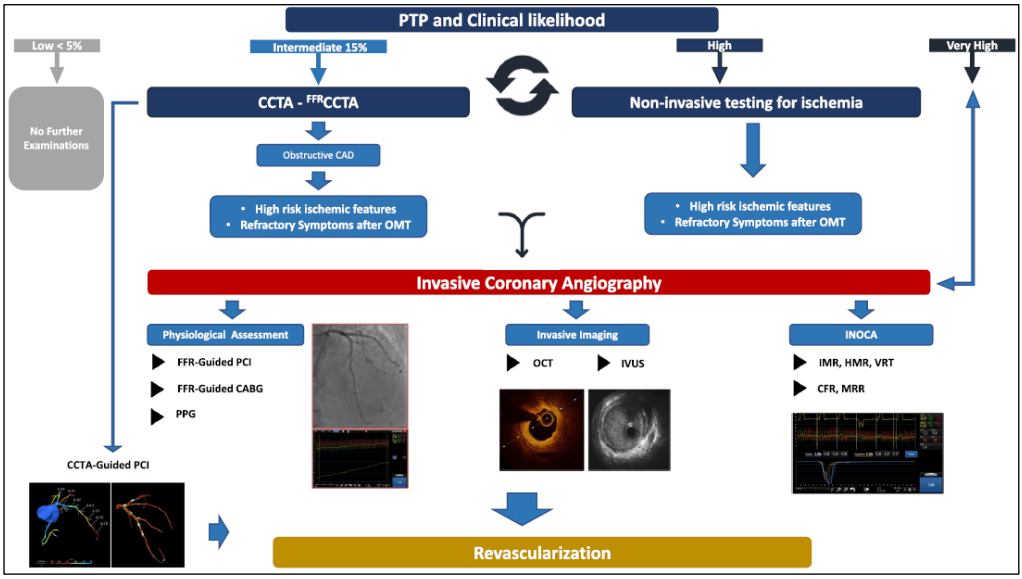

Figure 15. Diagnostic flowchart for non-invasive and invasive assessment. CCTA coronary computed tomography angiography, FFR fractional flow reserve, OMT optimal medical therapy, PPG pullback pressure gradient, OCT optical coherence tomography, IVUS intravascular ultrasound.

However, it is recommended in patients where the imaging tests are non-conclusive, and the clinical likelihood is very high, remembering that in clinical practice, approximately 30 to 70% ofpatient s with symptoms and/or signs of ischemia, referred to coronary angiography, have non obstructive coronary artery disease (INOCA) . In this contest, physiology and imaging-guided revascularization represent the cornerstone of contemporary management of chronic coronary syndromes (CCS) patients allowing us to focus specifically on ischemia-inducing stenoses[2]. Finally, we also discuss contemporary medical therapeutic approach for secondary prevention. The aim of this review is to provide an updated diagnostic and therapeutic approach for the management of patients with stable coronary artery disease.

Part VII

Discussion and Conclusions

Discussion

Part I. Evolution of FFR from the "oldest" adenosine to the new saline continuous thermodilution: physiologycal mechanism and long-term prognostic impact.

Since its first description, FFR is considered the standard of reference for evaluation of the ischemic potential of coronary stenoses and the expected benefit from revascularization or as opposite to defer revascularization. Bearing this in mind, FFR-guided revascularization of intermediate lesions in patients with preserved LVEF is associated with improved clinical outcomes compared with the angiographic one. However, data on the impact of FFR in patients with heart failure are still limited despite the evidence of an effective tool in detecting hemodynamically significant coronary stenosis even in case of elevated filling pressures as in the moderate/severe LV ejection fraction. In the present study, we investigate the role of FFR in deferring revascularization by comparing long-term clinical outcomes in patients with reduced LVEF based on either angiography or FFR discovering that angiography plus invasive functional assessment with FFR is associated with lower rate of death and MACCE at 10 years of follow-up, compared with angiographic assessment[3]. Moreover, when the relation between the predicted probability of events with FFR and left ventricular ejection fraction were expressed as continuum, the benefit of deferring revascularization based on FFR is evident when the ejection fraction is >25% and tends to decrease for values below it. Because FFR CFR and IMR requiring hyperemia thought different drugs administration (intravenously or intracoronary), we tested and clarify, the mechanism behind the

hyperemia induction during intracoronary infusion of saline at room temperature. In order to prove this, we performed increasing infusion rates of saline at room temperature at 10 mL/min (resting phase), 20 mL/min (hyperemic phase) and 2 minutes after the cessation of infusion (post hyperemic phase) through the RayFlow™ catheter in the LAD and simultaneously collected venous blood sample from the coronary sinus, previously incannulated, at each stage. Continuous thermodilution and subsequent absolute resting and hyperemic flow were measured in the LAD. During the study we have also observed that the intracoronary saline infusion does not affect blood pressure, systolic, or diastolic left ventricular functional and cardiac rhythm, resulting free from side or adverse event. Significant increased level of LDH and PFHb as well as the percentage of hemolysis at visual inspection of centrifugated blood sample only in the hyperemic phase, confirmed erythrocytes's lysis as the mechanism responsible of the hyperemia induction. Basically, the hemolysis of the erythrocytes, resulting from the mechanical action of the saline through the 4 side holes of the catheter in proximal epicardial segments, induces vasodilation of downstream resistance arteries by ATP and NO release after hemolysis with the subsequent dilatation due to the interaction with A2 receptor (endothelium-independent) or directly (endothelium-dependent)[4]. These findings have opened a new scenario in terms of microcirculatory assessment of flow and resistance using the RayFlow™ catheter, avoiding any specific pharmacological hyperemia.

Part II. New perspective in thermodilution-based coronary physiology: evaluation of different technique.

Coronary microvascular disfunction (CMD) is associated with anginal complaints, reduced quality of life, and a worse prognosis even with complete epicardial healthy vessels. Due to this, the evaluation of the IMR and CFR has been established for the diagnosis of INOCA/ANOCA. According with the common physiologic principes based on thermodilution both the method bolus and continuous are validated to microvascular assessment. Comparing with continuous thermodilution, the bolus technique estimates IMR by combining distal coronary pressure and indirect indices of flow, such as mean transit time. For its ease of application and its outcome prediction capacity in the acute coronary syndromes and INOCA/ANOCA settings, bolus thermodilution assessment is the most widespread in the current clinical practice, emerging as one of the reference standards to define CMD. In the last years, continuous thermodilution provides a direct measurement of flow (Q) and resistance (R) obtaining, as consequence, the microvascular resistance reserve (MRR) index which has the advantage to be completely independent from epicardial resistance and thus coronary stenosis. The studies presented in this paragraph aim to investigating the reproducibility of the bolus vs continuous thermodilution to assess flow (CFR vs Q) and resistance (IMR vs MRR) in ANOCA patients. Because of the direct volumetric measurements of flow and the operator independency, our results shown the superiority of continuous method in assessing coronary microcirculation in terms of accuracy and variability[5,6]. Clinical implication of the discrepancy between the two techniques can affect the diagnosis of

CMD due to the overestimation of CFR $_{bolus}$ and IMR $_{bolus,}$ with an underdiagnosed rates estimates in approximately 30% of the cases. Finally, also test-retest reliability demonstrate the higher accuracy of the continuous thermodilution with an agreement >95% between the measurements. Considering the previous evidences and the advantage of the saline induced hyperemia instead of pharmacological one (papaverine, adenosine ecc), continuous thermodilution might be the method of choice despite the cost and the need of additional material, as pump for controlled saline infusion and Rayflow catheter.

Part III. Pattern characterization and prognostic values of a comprehensive coronary circulation assessment: when and how.

Bolus and continuous thermodilution for coronary circulation assessment, have many useful features: 1) complete investigation of epicardial and microcirculation in the same procedure with no more than 10-15 minutes ; 2) the possibility of coronary flow (CFR or Q) and resistance (IMR or R) measurements with proven prognostic evidence; 3) allow to describe coronary circulation status in different pattern of disease (aortic stenosis, diabetic patients, HErEF, HEpEF) understanding the physiologic abnormalities behind it; 4) extend the diagnostic spectrum to diseases as CMD (functional or structural), responsible of more than 30% of angina with normal epicardial vessels. Often, mismatch between symptoms and absence of coronary vessels disease, lead to multiple coronary angiographies during the years underestimate the value of the microcirculation investigations. Furthermore, for continuous thermodilution technique, additional advantages regard 1) low variability due to the completely intra and inter-operator variability 2) saline induced hyperemia

without hyperemic agent administration and the side effects correlated; 3) independence of MRR from epicardial stenosis and myocardial mass; 4) direct volumetric quantification of coronary flow. Given the opportunity of complete coronary assessment derived from the technological progress, we start to investigate and describes the main characteristics across the most common cardiovascular disease.

Focusing on diabetic patients, we discovered the impairment of CFR and MRR with a prevalence of subclinical diastolic disfunction (low LASr) in these population comparing with the non-diabetic. Specifically, in our study we found a CFR <2.5 in 40% of the population with lower MRR in DM patients suggesting an impairment of both hyperemic flow (with increased R_{hyp}) and increased basal flow (with decreased R_{rest}). Interestingly, in DM patients, low values of FFR compared with % of diameter stenosis are probably leading to the diffuseness of epicardial stenosis. However, as explained previously, adopting MRR, we eliminate the influence of epicardial disease and myocardial mass[7].

Concerning the aortic stenosis (AS), our line of research focused on the compensatory mechanism of coronary circulation driven by the low cardiac output and LV hypertrophy typical of this disease. Beyond the pure physiological description, this topic has also high clinical importance in the reliability of FFR measurements in intermediate coronary stenosis in AS patients and in predicting LV remodeling after TAVR or AVR. Using continuous thermodilution, we tried to explain the interplay between coronary flow and myocardial mass. We found an increased absolute resting flow (Q_{rest}) but not the hyperemic one (Q_{hyp}) leading to a reduction of both CFR and MRR in this population. According with this findings, also myocardial perfusion (ml/min/mg) during hyperemia results in lower value

compared with the no-AS cohort. Since the hyperemic flow cannot further increase, this evidence suggests a baseline increase of resting flow resulting in CFR reduction. This “baseline hyperemic status” characterized by vasodilatation and low microvascular resistance, represents the compensatory mechanism of the coronary autoregulation to maintain constant resting perfusion. The increase in LV pressure and LV hypertrophy had a trade-off in terms of additional oxygen demand, contributing to a shift in coronary flow from the endocardium to the epicardium, leading to subendocardial ischemia[8]. On the clinical side, ischemia-related mismatch, are responsible of the angina onset reflecting the overcome compensatory limits of coronary autoregulation and represents a red flag for AS progression and severity. Knowing the physiological adaption of coronary circulation in AS patients, is questionable the reliability of resting and hyperemic index for intermediate coronary stenosis evaluation. The increase in resting flow may already be associated with some degree of microvascular dilation, whereas the decrease in hyperemic perfusion in LVH, may be changed after afterload reduction due to LV reverse remodeling after TAVR or AVR. Bearing this in mind, we investigated the variability of epicardial and microvascular index after 6 months of follow up, discovering no changes in resting/hyperemic flow and coronary flow reserve in the overall population, while an increase of hyperemic flow was found in patients with LV reverse remodeling. These findings support the evidence that the reverse remodeling play an important role in oxygen demand supply to the myocardium, even more than the acute LV unloading achieved with the valve replacement. Coronary autoregulation seems to be preserved before, immediately after and at 6 months follow up, underlining the complex relations between myocardial mass, coronary flow and

symptoms onset.

Heart failure (HF) is one of the most common causes of hospitalization all over the world, nevertheless physiologic evaluation of coronary circulation has never been fully investigated. According with these observations, we investigated the impact of CMD across HF patients, characterizing different pattern (functional vs structural CMD) by using continuous thermodilution. The identification of different physiological phenotype might provide further prognosis impact beyond the clinical classification of HFpEF and HFrEF based on LV function and filling pressure. Absolute coronary flow, absolute microvascular resistance, coronary flow reserve and microvascular resistance reserve seem to describe a prevalent functional CMD in HFrEF (lower R_{hyp} and higher Q_{rest}) whereas a structural CMD in HFpEF (higher R_{hyp} and lower Q_{rest}). While establishing causality remain challenging, common pathophysiological factors are recognisable. Diastolic disfunction and higher filling pressure in HFpEF, might be responsible of reduced hyperemic perfusion leading to subendocardial ischemia. In addition, ab extrinsic compression coming from LV hypertrophy results in abnormal microvascular response with lack of vasodilatation and increased R_{hyp} . Furthermore, fibrosis and systemic inflammation probably plays a fundamental role in the development of structural CMD, as suggests from higher level of ST-2 compare with No-CMD patients or patients with functional CMD in HFrEF. As opposite, functional CMD underlying distinct pathophysiological mechanism mainly driven by the neurohormonal systems activation. Increasing in oxygen myocardial demand caused by the rising in catecholamines level, will increase the Q_{rest} and reducing R_{rest} as adaptative mechanism, as well as the increased activity of nitric oxide synthase to compensate higher

metabolic request[9]. The differentiation of CMD patterns among HF phenotypes is not only nosological, but coronary physiological assessment helps us to understand the major abnormalities in flow and resistance and may predict LV remodeling and improvement in clinical symptoms during follow-up. To date, since we were able to recruit only few patients the relationship between CMD and lower LV reverse remodeling in HErEF patients, needs to be further investigated in order to highlight the prognostic impact of coronary physiology status in HF patients.

Conclusions

In this research journey we investigated: a) the prognostic role of FFR in functional evaluation of epicardial stenosis in patients with low ejection fraction; b) the mechanism behind the saline induced hyperemia; c) the technical and physiological difference in thermodilution based coronary physiology evaluation by an head to head comparison between bolus and continuous method; d) the role of IMR, CFR absolute coronary flow and microvascular resistances assessment with in different clinical scenario; Starting from the solid data proving the effectiveness and safety of FFR as milestone in functional assessment of the ischemic burden related to coronary stenoses, our results corroborate the born of new era of coronary physiology assessment. Absolute coronary blood flow (Q) and microvascular resistance (R) can be safely and reproducibly measured with continuous thermodilution, opening new opportunities for the study of the coronary microcirculation. Innovative method as continuous thermodilution might be help to understand the pathophysiology behind heart disease, giving a big step forward in the treatment of cardiovascular disorders.

We hope that after reading this thesis many questions arises, because exactly that has been the aim of my research, which is based on questions rather than answers. Behind every great discovery, someone asked the right question and, with patience and dedication, was able to find the answer over time.

List of abbreviations

CAD: coronary artery disease;

AS: Aortic stenosis;

DM: Diabetes mellitus;

FFR: fractional flow reserve;

PCI: percutaneous coronary intervention;

CFR: coronary flow reserve;

IMR: index of microcirculatory resistance;

Tmn: mean transit time;

MRR: Microvascular resistance reserve

CFR: Coronary flow reserve

Q: Absolute coronary flow;

R: Microvascular resistance;

DS: Diameter stenosis;

ANOCA: Angina and non-obstructive coronary artery disease;

NOCAD: Non-obstructive coronary artery disease;

CMD: Coronary microvascular disease;

HF: heart failure;

HFpEF: Heart failure with preserved ejection fraction

HFrEF: Heart failure with reduced ejection fraction

RCA: right coronary artery;

LAD: left anterior descending artery;

LCx: left circumflex artery;

MACCE: major adverse cardiovascular and cerebrovascular events;

LVEF: Left ventricular ejection fraction;

ATP: Adenosine triphosphate;

LDH: Lactate dehydrogenase;

PFHb: Plasma free haemoglobin;

LASr: Left atrial reservoir strain;

LAS: Left atrial strain;

PTP: Pre-test probability;

CCTA: Coronary computed tomography angiography;

ICA: Invasive coronary angiography;

CCS: Chronic coronary syndromes;

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Name and type of organisation providing education and training	Hartcentrum - OLVZ Cardiovascular Center, Aalst – Belgium Directed by Prof Bernard De Bruyne
Dates	**17/10/2019**
Title of qualification awarded	**Specialist in Cardiology** Discussing the experimental thesis entitled "*Short and medium-term outcomes of antithrombotic therapy in patients undergoing TAVI: which drug for which patient*"; Tutor Doctors Oliva Fabrizio, Oreglia Jacopo Andrea and D'Agostino Carlo.
Final vote	**70/70 cum laude**

Name and type of organisation providing education and training	**ASST Grande Ospedale Niguarda Cardio Center, Milan, Italy** Division of Interventional cardiology direct by Dr Jacopo Oreglia, Division of cardiac intensive care unit (CCU) directed by Dr Fabrizio Oliva
Dates	**September 2018 – January 2021**
Principal subjects/occupational skills covered	**Resident cardiology**
Name and type of organization providing education and training	**University Hospital Policlinico Consorziale, Bari, Italy** CCU in division of "Hospital Cardiology" directed by doctor Carlo D'Agostino ICU in Department of Anesthesia and Intensive care unit "A.Brienza" directed by Prof Francesco Bruno
Dates	**October 2017 – September 2018**
Principal occupational skills covered	**Cardiology Resident**

Dates	**September 2008 – October 2014**
Title of qualification awarded	**Degree in Medicine and Surgery.** Professor Concetta Torromeo and PE Puddu.
Name and type of organization providing education and training	**Sapienza University of Rome, Rome, Italy**.
Final vote	**110/110 cum laude**

Personal skills and competences

Mother tongue(s) Italian

Other language(s) English

Self-assessment	**Understanding**		**Speaking**		**Writing**
European level (*)	Listening	Reading	Spoken interaction	Spoken production	
English	C1	C1	C1	C1	C1

(*) Common European Framework of Reference for Languages

Social skills and competences: Volunteer of Italian Red Cross (CRI) local section of Rome.

Technical skills and competences: Coronary angiography, iFR and FFR measure, intracoronary imaging, right heart catheterization, setting of invasive and non invasive ventilation, central venous and arterial accesses, setting invasive and noninvasive hemodynamic monitoring. Management of critical cardiovascular ill patients

Computer skills and competences	European computer driving license (ECDL)
Other skills and competences	2015 Certified, Basic Life Support and Defibrillation (***BLSD***) (AHA) (Recertified 2017) 2015 Certified, Advanced Cardiac Life Support (***ACLS***) (AHA) (Recertified 2019) 2019 Certified, Advanced Cardiac Life Support for Experienced Providers (***ACLS EP***) (AHA) 2019 Attendance at Mechanical Ventilation course, "Le modalità di ventilazione meccanica", Fondazione Poliambulanza, Prof. G. Natalini 2019 Attendance at Mechanical Ventilation course, "Corso di Ventilazione Meccanica. "Dalla teoria alla pratica clinica" Fondazione Poliambulanza, Prof. G. Natalini
Driving licence	Italian driving license of type B and type A1
Additional information	
Memberships	2018 Italian Society of Cardiology (SIC) 2017 Acute Cardiovascular Care Association (ACCA) 2017-2018 European Association of Cardiovascular Imaging (EACVI) 2019 Associazione nazionale medici cardiologi ospedalieri (ANMCO) 2019 Fellow in training Italian Society of Cardiology (SIC) 2024 EAPCI Member

Conference Presentations, Seminar and Course

1 "***Treatment of acute stent thrombosis guided by OCT***": **XPERT IN COMPLEX SETTINGS: ACS AND LM BIFURCATION PCI Imaging, stent and techniques,** Abbott Educational Network Cardiovascular, 13-14 September 2018, Rome, Italy. (selected clinical case)

2 **XPERT IN COMPLEX PATIENTS and LESION SETTINGS**: Imaging, stent and techniques, Abbott Educational Network Cardiovascular, 16-17 April 2019, Monza, Italy.

3 **ABCTO Course** director Gabriele Gasperini and Jacopo Andrea Oreglia , 4 days on CTO revascularization 24/01, 21/02, 13/03 and 9/04 -2024, Milan

Research Project

"MECHANICAL AND CLINICAL TOOLS FOR DETECTING HEART DISEASES IN HUMANS".
Puddu, Schiariti, Torromeo, Nardinocchi, Pezzulla, Piras, Esposito, Rossi, Evangelista, Gabriele, Teresi, Varano.
Sapienza University Research Grant N. C26A15JZ7K, 2015;

"MECHANICS OF THE ATRIO-VENTRICULAR COUPLING IN PHYSIOLOGICAL CONDITIONS AND IN PRESENCE OF DIASTOLIC DISFUNCTION".
Nardinocchi, Puddu, Schiariti, Torromeo, Piras, Esposito, Evangelista, Varano, Gabriele, Teresi.
Sapienza University Research Grant N. RM116154C8A44723, 2016;

"MECHANICS OF SOFT FIBERED ACTIVE MATERIALS".
Nardinocchi, Schiariti, Torromeo, Addessi, Ciambella, Piras, Dasilva, Di Re, Puddu, Esposito, Evangelista, Varano, Gabriele, Teresi .
Sapienza University Research Grant N. RG11715C7CE2C1C4, 2017.

"MECHANICAL INSIGHTS INTO VOLUME OVERLOADED LEFT HEART: TWO-CHAMBER DIASTOLIC-SYSTOLIC FUNCTIONAL DISEASES".
Sapienza University Research Grant N. *RM1181642B2FDE85, (2018).*

"COronary Re-EngageMent aFter RandOm NavitoR Alignment (COMFORT STUDY)"
ClinicalTrial.gov NCT05779787

"Ischemic And Bleeding Risk Assessment After TAVR (FOCUS ONE)"
ClinicalTrial.gov NCT06000943

List of Publications

PEER-REVIEWED MANUSCRIPTS

- *Piras P., Torromeo C., Re F., Evangelista A., Gabriele S., Esposito G., Nardinocchi P., Teresi L., Madeo A., Chialastri C., Schiariti M., Varano V., Uguccioni M., Puddu P.E.Left Atrial trajectory impairment in Hypertrophic Cardiomyopathy disclosed by Geometric Morphometrics and Parallel Transport (2016) Scientific Reports. DOI: 10.1038/srep34906*

- *Bermpeis K., Esposito G., Gallinoro E., Paolisso P., Bertolone D.T., Fabbricatore D., Mileva N., Munhoz D., Buckley J., Wyffels E., Sonck J., Collet C., Barbato E., De Bruyne B., Bartunek J., Vanderheyden M. Safety of Right and Left Ventricular Endomyocardial Biopsy in Heart Transplantation and Cardiomyopathy Patients (2022) JACC: Heart Failure. DOI: 10.1016/j.jchf.2022.08.005*

- *Paolisso P., Gallinoro E., Mileva N., Moya A., Fabbricatore D., Esposito G., De Colle C., Beles M., Spapen J., Heggermont W., Collet C., Van Camp G., Vanderheyden M., Barbato E., Bartunek J., Penicka M. Performance of non-invasive myocardial work to predict the first hospitalization for de novo heart failure with preserved ejection fraction (2022) ESC Heart Failure. DOI: 10.1002/ehf2.13740*

- *Soriano F., Montalto C., Calderone D., Nava S., Esposito G., Saia F., Oreglia J.A., Søndergaard L.Transcatheter treatment of severe aortic stenosis in patients with complex coronary artery disease: case series and proposed therapeutic algorithm (2022) European Heart Journal - Case Reports, DOI: 10.1093/ehjcr/ytac399*

- *Gabriele S., Teresi L., Varano V., Nardinocchi P., Piras P., Esposito G., Puddu P.E., Torromeo C., Evangelista A. Mechanics–based analysis of the left atrium via echocardiographic imaging (2016) Computational Vision and Medical Image Processing V - Proceedings of 5th Eccomas Thematic Conference on Computational Vision and Medical Image Processing, VipIMAGE 2015. DOI: 10.1201/b19241-*

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- *Paolisso P., Bergamaschi L., Gragnano F., Gallinoro E., Cesaro A., Sardu C., Mileva N., Foà A., Armillotta M., Sansonetti A., Amicone S., Impellizzeri A., Esposito G., Nuccia M., Andrea O.J., Casella G., Mauro C., Vassilev D., Galie N., Santulli G., Marfella R., Calabrò P., Pizzi C., Barbato E.*

- *Outcomes in diabetic patients treated with SGLT2-Inhibitors with acute myocardial infarction undergoing PCI: The SGLT2-I AMI PROTECT Registry (2023) Pharmacological Research. DOI: 10.1016/j.phrs.2022.106597*

- *Piras P., Teresi L., Gabriele S., Evangelista A., Esposito G., Varano V., Torromeo C., Nardinocchi P., Puddu P.E. Systo-diastolic LV shape analysis by geometric morphometrics and parallel transport highly discriminates myocardial infarction (2016) Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics). DOI: 10.1007/978-3-319-28712-6_13*

- *Gallinoro E., Paolisso P., Candreva A., Bermpeis K., Fabbricatore D., Esposito G., Bertolone D., Peregrina E.F., Munhoz D., Mileva N., Penicka M., Bartunek J., Vanderheyden M., Wyffels E., Sonck J., Collet C., Debruyne B., Barbato E. Microvascular Dysfunction in Patients With Type II Diabetes Mellitus: Invasive Assessment of Absolute Coronary Blood Flow and Microvascular Resistance Reserve (2021) Frontiers in Cardiovascular Medicine. DOI: 10.3389/fcvm.2021.765071*

- *Paolisso P., Gallinoro E., Belmonte M., Bertolone D.T., Bermpeis K., De Colle C., Shumkova M., Leone A., Caglioni S., Esposito G., Fabbricatore D., Moya A., Delrue L., Penicka M., De Bruyne B., Barbato E., Bartunek J., Vanderheyden M. Coronary Microvascular Dysfunction in Patients With Heart Failure: Characterization of Patterns in HFrEF Versus HFpEF (2024) Circulation: Heart Failure DOI: 10.1161/CIRCHEARTFAILURE.123.010805*

- *Wyffels E., Beles M., Baeyens A., Croeckaert K., De Potter T., Van Camp G., Collet C., Sonck J., Vanderheyden M., Bartunek J., Barbato E., Bermpeis K., Bertolone D.T., Gallinoro E., Esposito G., Schoonjans G., Staelens F., Van Laer E., De Bruyne B. Same Day Discharge Strategy by Default in a Tertiary Catheterization Laboratory. Value Based Healthcare-Change in Practice. (2023) Health Policy. DOI: 10.1016/j.healthpol.2023.104826*

- *Piras P., Colorado-Cervantes I., Nardinocchi P., Gabriele S., Varano V., Esposito G., Teresi L., Torromeo C., Puddu P.E. Geometry Does Impact on the Plane Strain Directions of the Human Left Ventricle, Irrespective of Disease (2022) Journal of Cardiovascular Development and Disease DOI: 10.3390/jcdd9110393*

- *Esposito G., Piras P., Evangelista A., Nuzzi V., Nardinocchi P., Pannarale G., Torromeo C., Puddu P.E. Improving performance of 3D speckle tracking in arterial hypertension and paroxysmal atrial fibrillation by using novel strain parameters (2019) Scientific Reports. DOI: 10.1038/s41598-019-43855-7.*

- *Bertolone D.T., Bermpeis K., Gallinoro E., Esposito G., Paolisso P., De Colle C., Sonck J., Collet C., De Bruyne B., Barbato E., Van Praet F., Wyffels E. First report of totally robotically assisted hybrid coronary artery revascularization combining RE-MIDCAB and R-PCI: Case report (2022) Journal of Cardiac Surgery. DOI: 10.1111/jocs.16674*

- *Paolisso P., Bergamaschi L., Gragnano F., Gallinoro E., Cesaro A., Sardu C., Mileva N., Foà A., Armillotta M., Sansonetti A., Amicone S., Impellizzeri A., Esposito G., Morici N., Andrea O.J., Casella G., Mauro C., Vassilev D., Galie N., Santulli G., Marfella R., Calabrò P., Barbato E., Pizzi C.*

- *Reply to SGLT-2 inhibitors: Post-infarction interventional effects. (2023) Pharmacological Research, 189, art. no. 106664, Cited 0 times. DOI: 10.1016/j.phrs.2023.106664*

- *Wyffels E., Beles M., Baeyens A., Croeckaert K., De Potter T., Van Camp G., Collet C., Sonck J., Vanderheyden M., Bartunek J., Barbato E., Bermpeis K., Bertolone D.T., Gallinoro E., Esposito G., Schoonjans G., Staelens F., Van Laer E., De Bruyne B. Corrigendum to ' Same Day Discharge Strategy by Default in a Tertiary Catheterization Laboratory. Value Based Healthcare-Change in Practice.' Health Policy. DOI: 10.1016/j.healthpol.2023.104829*

- *Morici N., Cantoni S., Soriano F., Sacco A., Viola G., Esposito G., Oreglia J.A., Cattaneo M., Savonitto S. Recurrent stent thrombosis in a patient with acute coronary syndrome and ischemic colitis: between life-threatening thrombosis and life-threatening bleeding. (2020) Platelets. DOI: 10.1080/09537104.2019.1678122*

- *Piras P., Torromeo C., Evangelista A., Gabriele S., Esposito G., Nardinocchi P., Teresi L., Madeo A., Schiariti M., Varano V., Puddu P.E. Homeostatic Left Heart integration and disintegration links atrio-ventricular covariation's dyshomeostasis in Hypertrophic Cardiomyopathy (2017) Scientific Reports. DOI: 10.1038/s41598-017-06189-w*

- *Morelli M., Galasso M., Esposito G., Soriano F.S., Nava S., Da Pozzo C., Bossi I., Piccaluga E., Bruschi G., Maloberti A., Oliva F., Oreglia J.A., Giannattasio C., Montalto C. Natural history and clinical burden of moderate aortic stenosis: a systematic review and explorative meta-analysis.(2023) Journal of Cardiovascular Medicine. DOI: 10.2459/JCM.0000000000001490*

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- *Gallinoro E., Candreva A., Fernandez-Peregrina E., Bailleul E., Meeus P., Sonck J., Bermpeis K., Bertolone D.T., Esposito G., Paolisso P., Heggermont W., Adjedj J., Barbato E., Collet C., De Bruyne B. Saline-induced coronary hyperemia with continuous intracoronary thermodilution is mediated by intravascular hemolysis (2022) Atherosclerosis. DOI: 10.1016/j.atherosclerosis.2022.05.011*

- *Paolisso P., Gallinoro E., Andreini D., Mileva N., Esposito G., Bermpeis K., Bertolone D.T., Munhoz D., Belmonte M., Fabbricatore D., Sonck J., Collet C., Penicka M., De Bruyne B., Vanderheyden M., Barbato E. Prospective evaluation of the learning curve and diagnostic accuracy for Pre-TAVI cardiac computed tomography analysis by cardiologists in training: The LEARN-CT study (2022) Journal of Cardiovascular Computed Tomography. DOI: 10.1016/j.jcct.2022.03.002*

- *Cesaro A., Gragnano F., Paolisso P., Bergamaschi L., Gallinoro E., Sardu C., Mileva N., Foà A., Armillotta M., Sansonetti A., Amicone S., Impellizzeri A., Esposito G., Morici N., Oreglia J.A., Casella G., Mauro C., Vassilev D., Galie N., Santulli G., Pizzi C., Barbato E., Calabrò P., Marfella R.In-hospital arrhythmic burden reduction in diabetic patients with acute myocardial infarction treated with SGLT2-inhibitors: Insights from the SGLT2-I AMI PROTECT study (2022) Frontiers in Cardiovascular Medicine. DOI: 10.3389/fcvm.2022.1012220*

- *Gallinoro E., Paolisso P., Bermpeis K., Tino Bertolone D., Esposito G., De Bruyne B. When "Slow Flow" Is Not "Low Flow"(2022) JACC: Cardiovascular Interventions. DOI: 10.1016/j.jcin.2022.02.015*

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- *Morici N., Cantoni S., Soriano F., Viola G., De Stefano V., Veas N., Oreglia J.A., Esposito G., Sacco A., Savonitto S. Relevance of complete blood count parameters in the assessment of acute coronary syndromes: a combined hematological and cardiological perspective [Alterazioni dell'emocromo nella sindrome coronarica acuta: ematologi e cardiologi a confronto](2019). Giornale italiano di cardiologia (2006). DOI: 10.1714/3271.32379*

- *Crimi G., De Marzo V., De Marco F., Conrotto F., Oreglia J., D'ascenzo F., Testa L., Gorla R., Esposito G., Sorrentino S., Spaccarotella C., Soriano F., Bruno F., Vercellino M., Balbi M., Morici N., Indolfi C., De Ferrari G.M., Bedogni F., Porto I. Acute Kidney Injury After Transcatheter Aortic Valve Replacement Mediates the Effect of Chronic Kidney Disease (2022). Journal of the American Heart Association. DOI: 10.1161/JAHA.121.024589*

- *Paolisso P., Bergamaschi L., Cesaro A., Gallinoro E., Gragnano F., Sardu C., Mileva N., Foà A., Armillotta M., Sansonetti A., Amicone S., Impellizzeri A., Belmonte M., Esposito G., Morici N., Andrea Oreglia J., Casella G., Mauro C., Vassilev D., Galie N., Santulli G., Calabrò P., Barbato E., Marfella R., Pizzi C. Impact of SGLT2-inhibitors on contrast-induced acute kidney injury in diabetic patients with acute myocardial infarction with and without chronic kidney disease: Insight from SGLT2-I AMI PROTECT registry. (2023) Diabetes Research and Clinical Practice. DOI: 10.1016/j.diabres.2023.110766.*

- *Gallinoro E., Bertolone D.T., Fernandez-Peregrina E., Paolisso P., Bermpeis K., Esposito G., Gomez-Lopez A., Candreva A., Mileva N., Belmonte M., Mizukami T., Fournier S., Vanderheyden M., Wyffels E., Bartunek J., Sonck J., Barbato E., Collet C., De Bruyne B. Reproducibility of bolus versus continuous thermodilution for assessment of coronary microvascular function in patients with ANOCA (2023) EuroIntervention. DOI: 10.4244/EIJ-D-22-00772.*

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- *Paolisso P., Gallinoro E., Vanderheyden M., Esposito G., Bertolone D.T., Belmonte M., Mileva N., Bermpeis K., De Colle C., Fabbricatore D., Candreva A., Munhoz D., Degrieck I., Casselman F., Penicka M., Collet C., Sonck J., Mangiacapra F., De Bruyne B., Barbato E. Absolute coronary flow and microvascular resistance reserve in patients with severe aortic stenosis (2022) Heart. DOI: 10.1136/heartjnl-2022-321348*

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- *Gallinoro E., Paolisso P., Gioia G.D., Bermpeis K., Fernandez-Peregrina E., Candreva A., Esposito G., Fabbricatore D., Bertolone D.T., Bartunek J., Vanderheyden M., Wyffels E., Sonck J., Collet C., De Bruyne B., Barbato E. Deferral of Coronary Revascularization in Patients With Reduced Ejection Fraction Based on Physiological Assessment: Impact on Long-Term Survival (2022) Journal of the American Heart Association. DOI: 10.1161/JAHA.122.026656*

- *Esposito G., Barbato E., Bartunek J. Burden of In-Stent Restenosis: Shall We Overcome? (2021) Circulation: Cardiovascular Interventions. DOI: 10.1161/CIRCINTERVENTIONS.121.011292*

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