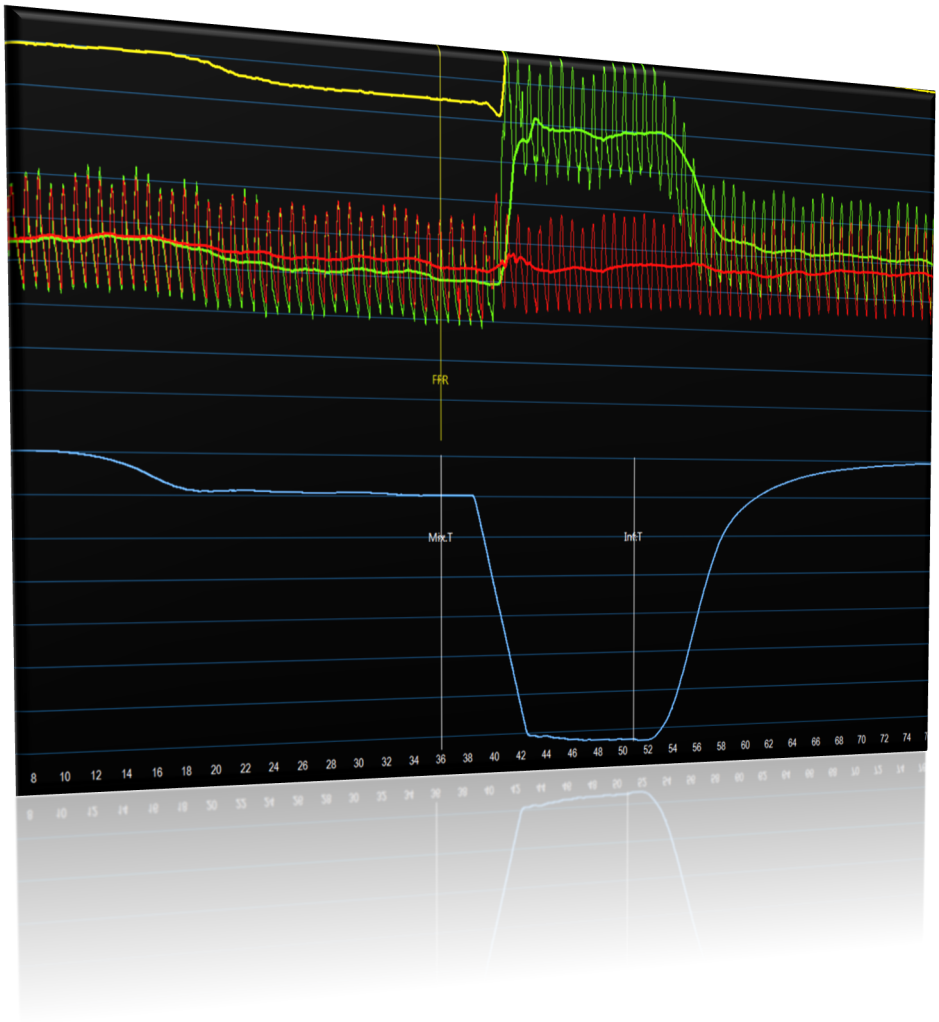
International PhD program in Cardiovascular Pathophysiology and Therapeutics – CardioPaTh



Coronary physiology: From new evidence supporting clinical benefit to new less invasive technologies

Dr Stephane Fournier, MD

Coronary physiology: From new evidence supporting clinical benefit to new less invasive technologies

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“Do what you love, and you’ll never

work another day in your life”

To
Anne, Marion & Maxime

With a Warm Thank You To
Olivier, Bernard & Emanuele

Table of content

LIST OF ABBREVIATIONS

1.	ACS	Acute Coronary Syndrome
2.	CABG	Coronary Artery Bypass Graft
3.	CAD	Coronary Artery Disease
4.	CFR	Coronary Flow Reserve
5.	CT	Computed Tomography
6.	FCL	Future Culprit Lesions
7.	FFR	Fractional Flow Reserve
8.	IMR	Index of Microvascular Resistance
9.	LAD	Left Anterior Descending (coronary artery)
10.	LCX	Left Circumflex (coronary artery)
11.	LMCA	Left Main Coronary Artery
12.	LVEF	Left Ventricular Ejection Fraction
13.	MACE	Major Adverse Cardiovascular Events
14.	MACCE	Major Adverse Cardiovascular and Cerebrovascular Events
15.	MI	Myocardial Infarction
16.	MT	Medical Treatment / Medical Therapy
17.	NCL	Non-Future Culprit Lesions
18.	NHPRs	Non-Hyperemic Pressure Ratios
19.	NSTE-ACS	Acute Coronary Syndrome without ST Segment Elevation
20.	PCI	Percutaneous Coronary Intervention
21.	Q	Flow
22.	R	Resistance
23.	RCA	Right Coronary Artery
24.	TAVI	Transcatheter Aortic Valve Implantation

MAIN ACHIEVEMENTS DURING THIS THESIS

- Fournier et al, JACC 2019:

  "In patients with significant stenoses (FFR≤0.80) but no angina, the rate of death or MI is higher than in patients with symptomatic ischemia. This difference is abolished by PCI".

- Fournier et al, JACC 2019:

  "These results confirm earlier animal data and demonstrate the linearity of the hyperemic pressure/ flow relationship during hyperemia in humans, thus confirming the theoretical background of FFR measurements".

- Fournier et al, JAMA Cardiol 2019:

  "The larger the improvement in FFR, the larger the symptomatic relief and the lower the event rate".

- Fournier et al, Circ Cardiovasc Int 2019:

  "In arterial grafts, FFR guidance was the only predictor of graft patency with a 3-fold probability of patent grafts at 6-year follow-up".

- Fournier et al, JAHA 2020:

  "Even in the absence of ischemia-producing stenoses, patients with a low global FFR present a higher risk of MACE at 5-year follow-up".

- Fournier et al, EuroIntervention 2021:

  "The present report provides reference values of absolute coronary hyperemic flow and resistances".

1. LIST OF PUBLICATIONS PER CHAPTER

During this PhD thesis, I had the opportunity to be involved in several projects leading to different publications (50 indexed on PubMed between November 1st 2018 and September 22nd 2021). Among them, 25 are discussed in this manuscript.

CHAPTER I : FFR : New evidences of clinical benefit

1. Zimmermann FM, Omerovic E, **Fournier S**, Kelbæk H , Johnson NP, Xaplanteris, P, Abdel-Wahab M, Barbato E, Høfsten DE, Boxma-de Klerk BM, Fearon WF, Køber L, Pieter C, Smits PC, De Bruyne B, Pijls NHJ MD, Engstrøm T
   Fractional Flow Reserve-Guided Percutaneous Coronary Intervention Versus Medical Therapy to Reduce Cardiac Death and Myocardial Infarction.
   Eur Heart J. 2019 Jan 7;40(2):180-186
   → **Manuscript reference: (1)**

2. **Fournier S,** Jüni P, De Bruyne B
   PCI Guided by Fractional Flow Reserve at 5 Years.
   N Engl J Med. 2019 Jan 3;380(1):104-105.
   → **Manuscript reference: (2)**

3. **Fournier S.,** Ciccarelli G., Toth GG, Milkas A., Xaplanteris P., Fearon WF., Pijls NHJ., Barbato E., De Bruyne B.
   Association of Improvement in Fractional Flow Reserve With Outcomes, Including Symptomatic Relief, After Percutaneous Coronary Intervention.
   JAMA Cardiol . 2019 Apr 1;4(4):370-374
   → **Manuscript reference: (3)**

4. **Fournier S** , Kobayashi Y, Fearon WF, Collet C, Roza da Costa B, Rioufol G, Pijls NHJ, Jüni P, De Bruyne B
Asymptomatic Patients with Abnormal Fractional Flow Reserve Treated with Medication Alone or with PCI
J Am Coll Cardiol. 2019 Sep 24;74(12):1642-1644.
→ **Manuscript reference: (4)**

5. Milkas A, Rueda-Ochoa OL, **Fournier S**, Muller O, Van Rooij, Franco OH, Collet C, Barbato E, Kavousi M, De Bruyne B
Ten-Year Survival After FFR-Guided Strategy in Isolated Proximal Left Anterior Descending Coronary Stenosis. Matched Comparison with Normal Individuals
J Am Coll Cardiol. 2019 Sep 10;74(10):1420-1421
→ **Manuscript reference: (5)**

6. Di Gioia G; De Bruyne B, Pellicano M, Bartunek J, Colaiori , Fiordelisi A, Canciello G, Xaplanteris P, **Fournier S**, Katbeh A, Franco D; Kodeboina M, Morisco C, Van Praet F, Casselman F, Degrieck I, Stockman B, Vanderheyden M; Barbato E
Fractional Flow Reserve in patients with reduced ejection fraction
Eur Heart J. 2020;41(17):1665-72.
→ **Manuscript reference: (6)**

7. **Fournier S**, *Collet C, Xaplanteris P, Zimmermann FM, Toth GG, Tonino PAL, Pijls NHJ, Colaiori I, Di Gioia G, Barbato E, Jüni P, Fearon WF, De Bruyne B.*
Global FFR Value Predicts 5-Year Outcomes in Patients with Coronary Atherosclerosis but Without Ischemia
J Am Heart Assoc. 2020;9(24):e017729.
→ **Manuscript reference: (7)**

8. Toth GG, De Bruyne B, Kala P, Ribichini FL, Casselman F, Ramos R, Piroth Z, **Fournier S,** Piccoli A, Van Mieghem C, Penicka M, Mates M, Nemec P, Van Praet F, Stockman B, Degriek I, Barbato E.
   Graft patency after FFR-guided versus angiography-guided coronary artery bypass grafting. The GRAFFITI trial.
   EuroIntervention. 2019 Dec 6;15(11):e999-e1005
   → **Manuscript reference: (8)**

9. **Fournier S,** Toth GG, Colaiori I, De Bruyne B, Barbato E
   Long-term patency of coronary artery bypass graftsafter Fractional Flow Reserve guided implantation
   Circ Cardiovasc Interv. 2019 May;12(5):e007712
   → **Manuscript reference: (9)**

10. Changes in surgical revascularization strategy after fractional flow reserve.
    Fournier S, Toth GG, De Bruyne B, Kala P, Ribichini FL, Casselman F, Ramos R, Piroth Z, Piccoli A, Penicka M, Mates M, Nemec P, Van Praet F, Stockman B, Degriek I, Pellicano M, Barbato E.
    Catheter Cardiovasc Interv. 2021 Apr 10. doi: 10.1002/ccd.29694. Online ahead of print.PMID: 33837987
    → **Manuscript reference: (10)**

CHAPTER II: Beyond pressure: the coronary artery absolute flow

1. **Fournier S,** Colaiori I, Di Gioia g, Mizukami T, De Bruyne B

   Hyperemic Pressure-Flow Relationship in Man

   J Am Coll Cardiol. 2019 Mar 19;73(10):1229-1230.

   → **Manuscript reference: (11)**

2. **Fournier S,** Keulards DCJ, van 't Veer M, Colaiori I, Di Gioia G, Zimmermann FM, Mizukami T, Nagumo S, Kodeboina M, El Farissi M, Zelis JM, Sonck J, Collet C, Pijls NHJ, De Bruyne B.

   Normal Values of Thermodilution-Derived Absolute Coronary Blood Flow and Microvascular Resistance in Humans.

   EuroIntervention. 2021 Jul 20;17(4):e309-e316

   → **Manuscript reference: (12)**

3. Adjedj J, Picard F, Collet C, Bruneval P, **Fournier S**, Bize A, Sambin L, Berdeaux A, Varenne O, De Bruyne B, Ghaleh B.

   Intracoronary Saline-Induced Hyperemia During Coronary Thermodilution Measurements of Absolute Coronary Blood Flow: An Animal Mechanistic Study.

   J Am Heart Assoc. 2020 Jul 21:e015793. doi: 10.1161/JAHA.120.015793.

   → **Manuscript reference: (13)**

4. Keulards DCJ*, **Fournier S***, van 't Veer M, Colaiori I, Zelis JM, El Farissi M, Zimmermann FM, Collet C, De Bruyne B, Pijls NHJ
   Computed tomographic myocardial mass compared with invasive myocardial perfusion measurement.
   * equally contributed
   Heart. 2020 Oct;106(19):1489-1494.
   → **Manuscript reference: (14)**

5. Basics of Coronary Thermodilution.
   Candreva A, Gallinoro E, van 't Veer M, Sonck J, Collet C, Di Gioia G, Kodeboina M, Mizukami T, Nagumo S, Keulards D, **Fournier S**, Pijls NHJ, De Bruyne B.
   JACC Cardiovasc Interv. 2021 Mar 22;14(6):595-605.
   → **Manuscript reference: (15)**

6. Candreva A, Gallinoro E, **Fournier S,** Izaga E, Finet G, De Bruyne B, Gutiérrez-Barrios A.
   Absolute Blood Flow in the Left Main Coronary Artery and Its Distribution.
   JACC Cardiovasc Interv. 2021 Feb 22;14(4):482-484.
   → **Manuscript reference: (16)**

7. Thermodilution-Derived Volumetric Resting Coronary Blood Flow Measurement in Humans.
   Gallinoro E, Candreva A, Colaiori I, Kodeboina M, **Fournier S,** Nelis O, Di Gioia G, Sonck J, van 't Veer M, Pijls NHJ, Collet C, De Bruyne B.
   EuroIntervention. 2021 Feb 2:EIJ-D-20-01092. doi: 10.4244/EIJ-D-20-01092
   Online ahead of print.PMID: 33528358
   → **Manuscript reference: (17)**

CHAPTER III: Beyond the wire : angiography-Derived FFR

1. Fearon WF, Achenbach S , Engstrom T , Assali A, Shlofmitz R , Jeremias A , **Fournier S** , Kirtane AJ, Kornowski R , Greenberg G , Jubeh R , Kolansky DM , McAndrew T , Dressler O, Maehara A , Matsumura M , Leon MB , De Bruyne B
   Accuracy of Fractional Flow Reserve Derived From Coronary Angiography
   Circulation. 2019 Jan 22;139(4):477-484.
   → **Manuscript reference: (18)**

2. Johnson NP, Mahaera A, Achenbach S, Engstrom T, Assali A, Jeremias A, **Fournier S**, De Bruyne B, Leon MB, Fearon WF
   Angiography-derived fractional flow reserve versus invasive non-hyperemic pressure ratios
   J Am Coll Cardiol. 2019 Jun 25;73(24):3232-3233.
   → **Manuscript reference: (19)**

3. Kobayashi Y, Collet C, Achenbach S, Engstrøm T, Assali A, Shlofmitz RA, **Fournier S**, Kirtane AJ, Ali ZA, Kornowski R, Leon MB, De Bruyne B, Fearon WF
   Diagnostic performance of angiography-based fractional flow reserve by patient and lesion characteristics
   EuroIntervention . 2021 Jul 20;17(4):e294-e300.
   → **Manuscript reference: (20)**

4. Rubimbura V, Guillon B, **Fournier S**, Amabile N, Chi Pan C, Combaret N, Eeckhout E, Kibler M, Silvain J, Wijns W, Schiele F, Muller O, Meneveau N, Adjedj J. Quantitative flow ratio virtual stenting and post stenting correlations to post stenting fractional flow reserve measurements from the DOCTORS (Does Optical Coherence Tomography Optimize Results of Stenting) study population.
   Catheter Cardiovasc Interv . 2020 Nov;96(6):1145-1153
   → **Manuscript reference: (21)**

5. Future culprit detection based on angiography-derived FFR.
   Pagnoni M, Meier D, Candreva A, Maillard L, Adjedj J, Collet C, Mahendiran T, Cook S, Mujcinovic A, Dupré M, Rubimbura V, Roguelov C, Eeckhout E, De Bruyne B, Muller O, **Fournier S.**
   Catheter Cardiovasc Interv. 2021 Apr 29. doi: 10.1002/ccd.29736. Online ahead of print.PMID: 33913606
   → **Manuscript reference: (22)**

CHAPTER IV: Beyond catheters use : FFR derived from CT

11. Tzimas G, Meier D, Monney P, Roguelov C, Skalisis I, Muller O, **Fournier S**, Qanadli SD

    CT-scan in cardiology in 2019 : central role and other applications

    Rev Med Suisse. 2019 May 22;15(652):1060-1066

    → **Manuscript reference: (23)**

12. Meier D, Depierre A, Topolsky A, Roguelov C, Dupré M, Rubimbura V, Eeckhout E, Qanadli SD, Muller O and **Fournier S**

    Computed tomography angiography for the diagnosis of coronary artery disease among patients undergoing transcatheter aortic valve implantation

    J Cardiovasc Transl Res, In press

    → **Manuscript reference: (24)**

13. Meier D, Skalidis I,De Bruyne B,Qanadli SD, Rotzinger D,Eeckhout E,Collet C,Muller O, **Fournier S.**

    Ability of FFR-CT to detect the absence of hemodynamically significant lesions in patients with high-risk NSTE-ACS admitted in the emergency department with chest pain, study design and rationale.

    Int J Cardiol Heart Vasc. 2020 Mar 5;27:100496.

    → **Manuscript reference: (25)**

2.INTRODUCTION

Fractional Flow Reserve (FFR) was introduced in the 1990s as an index of the physiological significance of a coronary stenosis (26). FFR represents the ratio of maximal blood flow in a stenotic artery as compared with normal maximal flow. In practice, during invasive coronary angiography, FFR is obtained by calculating the ratio of the distal coronary pressure to the aortic pressure (measured with a coronary pressure guidewire and a guiding catheter, respectively). Over time, the benefits of FFR-guided coronary revascularization have been well demonstrated (27, 28), leading to its incorporation into clinical guidelines (29).

However, FFR suffers from **several limitations that were sources of inspiration for this PhD thesis. These limitations have been divided into four chapters** addressing: 1) the lack of data supporting the benefit of FFR in terms of improving hard clinical endpoints and the lack of data supporting the benefit of FFR the field of coronary artery bypass graft surgery, 2) the absence of information obtained by FFR on the microcirculation, 3) the risks associated with maneuvering a pressure wire down a coronary artery and 4) the general risks associated with invasive coronary angiography.

Overview of the thesis

- **Chapter 1** will focus on the publications dedicated to the benefit of FFR guidance in terms of clinical benefits. Indeed, while the landmark FAME 2 trial demonstrated that in patients with stable coronary artery disease, an initial FFR-guided percutaneous coronary intervention (PCI) strategy was associated with a significantly lower rate of the primary composite end point of death, myocardial infarction, or urgent revascularization as compared to medical therapy alone, this benefit was mainly driven by a higher rate of urgent revascularization (30). After 5 years of follow-up, we demonstrated before the beginning of this thesis a borderline yet significant reduction in spontaneous myocardial infarction (28). Thus, we have been working on different projects aiming to prove the significant impact of FFR-guided PCI on hard endpoints, symptom relief and also in specific debated contexts such as patients with reduced left ventricular function. This chapter will also focus on publications dedicated to the use of FFR guidance in the context of coronary artery bypass graft (CABG) surgery. Indeed, as the vast majority of the FFR trials were focused on patients treated by PCI, its validity in the field of CABG remains to be proven.
- **Chapter 2** will focus on publications dedicated to a new technique (coronary continuous thermodilution) allowing, for the first time, the measurement of not only pressure but also absolute flow and resistance.
- **Chapter 3** will focus on publications dedicated to new and less invasive technologies permitting the estimation of FFR based on invasive coronary angiography only, without the need for crossing the lesion with a pressure wire.
- **Chapter 4** will focus on publications dedicated to even less invasive technologies allowing the estimation of FFR without invasive coronary angiography but rather based on CT.

3. CHAPTER I : FFR : New evidences of clinical benefit

Introduction and overview of Chapter 1

Even if FFR is recommended by both the European and American guidelines (29, 31) to evaluate the significance of a stenosis in the absence of documented ischemia, until recently, the benefit of FFR-guidance was mainly observed for composite endpoints (classically, the "major adverse cardiovascular endpoints" (MACE), encompassing urgent revascularizations, myocardial infarction and cardiovascular death). Thus, data supporting the benefit of FFR in terms of hard endpoints reduction were still missing. It was particularly the case in the 2-year follow-up of the FAME 2 trial (30). In this trial, 1220 patients with stable coronary artery disease had FFR measurements in every stenosis. Patients who had at least one stenosis with a significant FFR (≤0.80) were randomly assigned either to FFR-guided PCI plus medical therapy or to medical therapy alone. When all FFR were negative, the patients received medical therapy alone and were included in a registry. The primary end point was a composite of death from any cause, nonfatal myocardial infarction, or urgent revascularization. At 2 years, the rate of the primary end point was significantly lower in the PCI group than in the medical-therapy group (8.1% vs. 19.5%; P<0.001) but of note, this significant difference was driven by a lower rate of urgent revascularization in the PCI group (4.0% vs. 16.3%; P<0.001), while no significant between-group differences were observed in the rates of death and/or myocardial infarction. However, slowly, a trend toward a significant reduction in myocardial infarction was observed at the 5-year follow-up (28) that we published before the beginning of my PhD. Indeed, while there was no significant difference between the PCI group and the medical-therapy group in the rates of death (5.1% and 5.2%, respectively; hazard ratio, 0.98; 95% CI, 0.55 to 1.75), the differences regarding myocardial infarction were borderline significant (8.1% and 12.0%; hazard ratio, 0.66; 95% CI, 0.43 to 1.00). To overcome a possible sample size effect, we pooled 3 trials that compared FFR-guided PCI vs. medical therapy in patients with stable coronary lesions in order to perform a collaborative individual patient data meta-analysis using the hard and symbolic endpoint of cardiac death or MI as prespecified primary composite endpoint. The results presented in this thesis are the abstract of the following publication:

- Zimmermann FM, Omerovic E, **Fournier S**, Kelbæk H , Johnson NP, Xaplanteris, P, Abdel-Wahab M, Barbato E, Høfsten DE, Boxma-de Klerk BM, Fearon WF, Køber L, Pieter C, Smits PC, De Bruyne B, Pijls NHJ MD, Engstrøm T
  Fractional Flow Reserve-Guided Percutaneous Coronary Intervention Versus Medical Therapy to Reduce Cardiac Death and Myocardial Infarction.
  Eur Heart J. 2019 Jan 7;40(2):180-186

In this meta-analysis of the FAME 2, DANAMI-3-PRIMULTI and Compare-Acute trials (32-34) in which we analyzed the data of 2400 patients, we reported that FFR-guided PCI resulted in a reduction of the composite of cardiac death or MI as compared to medical therapy, which was driven by a decreased risk of MI (details hereafter).

Some criticisms arose regarding this trend toward a lower rate of myocardial infarction in the FFR-guided PCI group of FAME 2 (35). This was mainly related to the fact that FFR-guidance allows a decision at lesion level, while a myocardial infarction at follow-up is an endpoint at patient level. Accordingly, the demonstration that myocardial infarctions occurred at the exact position of a lesion significant by FFR remained to be done. Accordingly, all the narratives of the FAME 2 trials were analyzed in order to evaluate if the location of the myocardial infarctions matched the location of a stenosis which was evaluated by FFR at randomization. The results presented in this thesis are related to the following publication:

- **Fournier S,** Jüni P, De Bruyne B
  PCI Guided by Fractional Flow Reserve at 5 Years.
  N Engl J Med. 2019 Jan 3;380(1):104-105.

In this letter, we reported that 89% of the myocardial infarction of the FAME 2 medical therapy group occurred at the site of a lesion which was significant by FFR at randomization (details hereafter).

In addition, while these two publications seem to support that there might be a benefit of FFR-guidance in terms of reduction of hard endpoints, the other main indication for an intervention is the symptoms of the patients (36). During this thesis, efforts were made to produce data supporting the association of improvement in FFR with outcomes, including symptomatic relief and to investigate the effect of FFR-guided PCI in asymptomatic patients.

The results of these 2 investigations presented in this thesis are the abstracts of the following 2 publications:

- **Fournier S.,** Ciccarelli G., Toth GG, Milkas A., Xaplanteris P., Fearon WF., Pijls NHJ., Barbato E., De Bruyne B.
  Association of Improvement in Fractional Flow Reserve With Outcomes, Including Symptomatic Relief, After Percutaneous Coronary Intervention.
  JAMA Cardiol. 2019 Apr 1;4(4):370-374

- **Fournier S** , Kobayashi Y, Fearon WF, Collet C, Roza da Costa B, Rioufol G, Pijls NHJ, Jüni P, De Bruyne B
  Asymptomatic Patients with Abnormal Fractional Flow Reserve Treated with Medication Alone or with PCI
  J Am Coll Cardiol. 2019 Sep 24;74(12):1642-1644.

In the first publication (JAMA Cardiol), we pooled the FAME 1 (27) and FAME 2 (28) populations and reported that the larger the improvement in FFR with a PCI, the larger the symptomatic relief and the lower the event rate. Indeed, vessel-oriented clinical events were significantly more frequent in the lowest tertile of ΔFFR (FFR after PCI – FFR before PCI) while a significant association was observed between ΔFFR and symptomatic relief (details hereafter). In the second publication, (J Am Call Cardiol), we analyzed the MT group of FAME

2 and reported that the composite of death or MI was significantly higher in asymptomatic patients than in patients with symptomatic ischemia (details hereafter).

Furthermore, in some specific situations, the validity or even the usefulness of FFR have been challenged. In the case of a proximal stenosis in the left anterior descending (LAD) coronary artery, the need for a FFR measurement when the diameter stenosis is >50% or the safety of deferral when the lesion is significant by visual estimation but negative by FFR are frequent questions / concerns (this vessel being considered as prognostic). In another setting, among patients with reduced left ventricular function, the validity of FFR has also been challenged (concerns about the influence of elevated right filling pressures and lake of data on the safety and on the long-term impact of an FFR-guided management strategy in patients with left ventricular systolic dysfunction). These 2 situations have been investigated and the results presented in this thesis are the abstracts of the following 2 publications:

- Milkas A, Rueda-Ochoa OL, **Fournier S**, Muller O, Van Rooij, Franco OH, Collet C, Barbato E, Kavousi M, De Bruyne B
  Ten-Year Survival After FFR-Guided Strategy in Isolated Proximal Left Anterior Descending Coronary Stenosis. Matched Comparison with Normal Individuals
  J Am Coll Cardiol. 2019 Sep 10;74(10):1420-1421

- Di Gioia G; De Bruyne B, Pellicano M, Bartunek J, Colaiori , Fiordelisi A, Canciello G, Xaplanteris P, **Fournier S**, Katbeh A, Franco D; Kodeboina M, Morisco C, Van Praet F, Casselman F, Degrieck I, Stockman B, Vanderheyden M; Barbato E
  Fractional Flow Reserve in patients with reduced ejection fraction
  Eur Heart J. 2019 Aug 16. pii: ehz571.

In the first publication (J Am Coll Cardiol), we reported that in patients with an isolated stenosis in the proximal LAD, medical therapy of FFR-negative stenoses and revascularization of FFR-positive stenoses is associated with similar survival rates. In the second publication (Eur Heart

J), we reported that in patients with reduced LVEF and CAD, FFR-guided revascularization was associated with lower rates of death and MACCE at 5 years as compared with an angiography-guided strategy.

Finally, it has been demonstrated in patients with stable coronary disease that the FFR-value (marker of stenosis severity) is a major and independent predictor of lesion-related outcome (37). However, there results are mainly driven by lesions significant by FFR (with a poor outcome) and whether it is true or not among a population of non-ischemic patients remained unknown. It has been addressed in a pooled FAME 1 and FAME 2 study. The abstract of the following publication is presented in this thesis:

- **Fournier S**, Collet C, Xaplanteris P, Zimmermann FM, Toth GG, Tonino PAL, Pijls NHJ, Colaiori I, Di Gioia G, Barbato E, Jüni P, Fearon WF, De Bruyne B.
  Global FFR Value Predicts 5-Year Outcomes in Patients with Coronary Atherosclerosis but Without Ischemia
  J Am Heart Assoc. 2020 Dec 15;9(24):e017729.

In this publication based on >1000 patients without significant stenoses or with significant stenoses successfully treated by PCI (with post-PCI FFR measurements done), we reported that even in the absence of ischemia-producing stenoses, patients with a low global FFR (sum of FFR in the 3 vessels) present a higher risk of MACE at 5-year follow-up. In this study, an increase in global FFR of 0.1 unit was associated with a significant reduction in the rates of MACE, myocardial infarction and revascularization (details hereafter).

We discussed so far in this chapter the benefits of FFR-guided revascularization in patients with stable coronary artery disease. However, while this concept has been extensively investigated and validated for percutaneous revascularization, whether FFR assessment of stenoses as compared to the traditional angiographic evaluation is also related to better

outcomes in patients undergoing coronary artery bypass graft surgery remains debated. Before the beginning of my PhD, we reported that FFR-guided CABG surgery is associated with a significant reduction in the rate of overall death or myocardial infarction at 6-year follow-up as compared to angiography-guided CABG surgery (38). However, these data were retrospective and thus, a trial was mandatory. In this context, the GRAFFITI trial was designed. The main results as well as a sub study investigating the changes in surgical revascularization strategy after FFR knowledge are presented hereafter and come from 2 publications:

- Toth GG, De Bruyne B, Kala P, Ribichini FL, Casselman F, Ramos R, Piroth Z, **Fournier S,** Piccoli A, Van Mieghem C, Penicka M, Mates M, Nemec P, Van Praet F, Stockman B, Degriek I, Barbato E.
  Graft patency after FFR-guided versus angiography-guided coronary artery bypass grafting. The GRAFFITI trial.
  EuroIntervention. 2019 Dec 6;15(11):e999-e1005

In this trial where 172 patients were randomized either to the angiography-guided group or to the FFR-guided group, the FFR-guided group received fewer anastomoses and at 1-year angiographic follow-up, no difference in overall graft patency was observed.

- **Fournier S,** Toth GG, De Bruyne B, Kala P, Ribichini FL, Casselman F, Ramos R, Piroth Z, Piccoli A, Penicka M, Mates M, Nemec P, Van Praet F, Stockman B, Degriek I, Pellicano M, Barbato E.Catheter
  Changes in surgical revascularization strategy after fractional flow reserve.
  Cardiovasc Interv. 2021 Apr 10. doi: 10.1002/ccd.29694.

In this GRAFFITI sub-study, the intended and performed strategy (before and after FFR) were compared and we reported that FFR-guided CABG is associated with a simplified surgical procedure in 55% of the patients, with similar clinical outcomes.

Finally, in order to further demonstrate the benefit of FFR-guidance for CABG surgery, we decided to analyze our 6-year follow-up of patients undergoing FFR-guided or angiography-guided CABG but at a graft level. The results of this study presented hereafter are based on the following publication:

- **Fournier S**, Toth GG, Colaiori I, De Bruyne B, Barbato E
  Long-term patency of coronary artery bypass grafts after Fractional Flow Reserve guided implantation
  Circ Cardiovasc Interv. 2019 May;12(5):e007712

In this study, the occlusion rate was significantly lower in the FFR-guided as compared with the angiography-guided group.

Zimmermann FM, Omerovic E, **Fournier S**, Kelbæk H , Johnson NP, Xaplanteris, P, Abdel-Wahab M, Barbato E, Høfsten DE, Boxma-de Klerk BM, Fearon WF, Køber L, Pieter C, Smits PC, De Bruyne B, Pijls NHJ MD, Engstrøm T

Fractional Flow Reserve-Guided Percutaneous Coronary Intervention Versus Medical Therapy to Reduce Cardiac Death and Myocardial Infarction.

Eur Heart J. 2019 Jan 7;40(2):180-186

Aims

To assess the effect of fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) with contemporary drug-eluting stents on the composite of cardiac death or myocardial infarction (MI) vs. medical therapy in patients with stable coronary lesions.

Methods and results

We performed a systematic review and meta-analysis of individual patient data (IPD) of the three available randomized trials of contemporary FFR-guided PCI vs. medical therapy for patients with stable coronary lesions: FAME 2 (NCT01132495), DANAMI-3-PRIMULTI (NCT01960933), and Compare-Acute (NCT01399736). FAME 2 enrolled patients with stable coronary artery disease (CAD), while the other two focused on non-culprit lesions in stabilized patients after acute coronary syndrome. A total of 2400 subjects were recruited from 54 sites world-wide with 1056 randomly assigned to FFR-guided PCI and 1344 to medical therapy. The pre-specified primary outcome was a composite of cardiac death or MI. We included data from extended follow-ups for FAME 2 (up to 5.5 years follow-up) and DANAMI-3-PRIMULTI (up to 4.7 years follow-up).

After a median follow-up of 35 months (IQR 12-60 months), a reduction in the composite of cardiac death or MI was observed with FFR-guided PCI as compared with medical therapy (hazard ratio 0.72, 95% confidence interval 0.54-0.96; P = 0.02). The difference between groups was driven by MI.

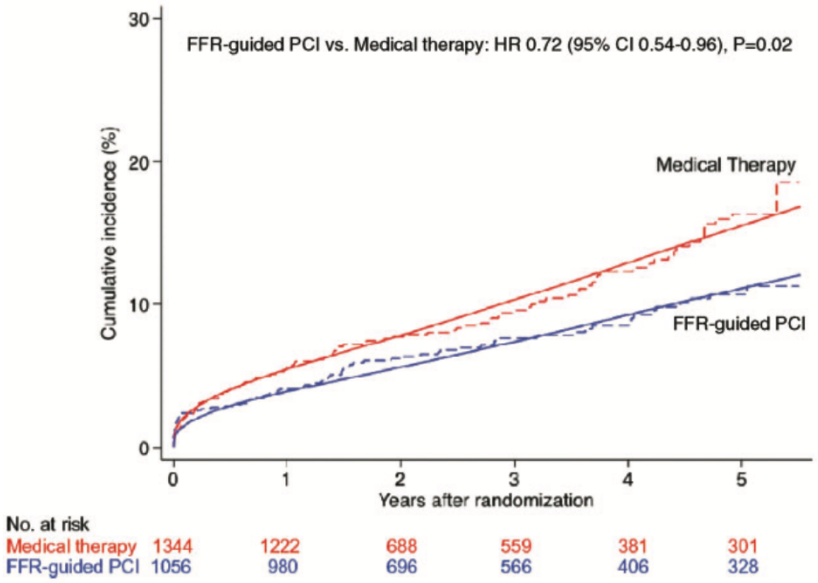


Figure 1

Conclusion

In this IPD meta-analysis of the three available randomized controlled trials to date, FFR-guided PCI resulted in a reduction of the composite of cardiac death or MI compared with medical therapy, which was driven by a decreased risk of MI.

Fournier S, Jüni P, De Bruyne B

PCI Guided by Fractional Flow Reserve at 5 Years.

N Engl J Med. 2019 Jan 3;380(1):104-105.

Bogaty correctly points out that a myocardial infarction could have occurred anywhere along the coronary vasculature. However, for each reported ischemic event, the FAME 2 investigators were requested to produce a narrative, including a description of the angiogram if available. On the basis of these narratives, we could identify the culprit lesion for 36 of the 53 myocardial infarctions reported as one of the components of the primary outcome in patients in the medical-therapy group of the FAME 2 trial, and we found that 32 of these lesions (89%) were hemodynamically significant, with an FFR of 0.80 or less. Our data therefore do not support the contention that abrupt occlusions occur predominantly in mild stenoses.

Fournier S., Ciccarelli G., Toth GG, Milkas A., Xaplanteris P., Fearon WF., Pijls NHJ., Barbato E., De Bruyne B.

Association of Improvement in Fractional Flow Reserve With Outcomes, Including Symptomatic Relief, After Percutaneous Coronary Intervention.

JAMA Cardiol. 2019 Apr 1;4(4):370-374

Importance

Whether the improvement in myocardial perfusion provided by percutaneous coronary intervention (PCI) is associated with symptomatic relief or improved outcomes has not been well investigated.

Objective

To investigate the prognostic value of the improvement in fractional flow reserve (FFR) after PCI (ΔFFR) on patients' symptoms and 2-year outcomes.

Design, setting, and participants

This study is a post hoc analysis of data from patients undergoing FFR-guided PCI in the randomized clinical trials Fractional Flow Reserve vs Angiography for Multivessel Evaluation (FAME) 1 (NCT00267774; 2009) and FAME 2 (NCT01132495; 2012), with inclusion of 2 years of follow-up data. The FAME 1 trial included patients with multivessel coronary artery disease from 20 medical centers in Europe and the United States. The FAME 2 trial included patients with stable coronary artery disease involving up to 3 vessels from 28 sites in Europe and North America. Lesions from the group in the FAME 1 trial from whom FFR was measured and the group in the FAME 2 trial who received FFR-guided PCI plus medical therapy were analyzed. Data analysis occurred from May 2017 to May 2018.

Interventions:

Measure of post-PCI FFR.

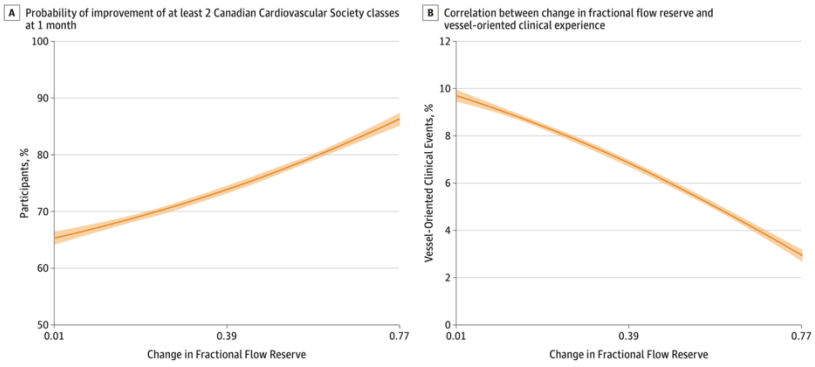
Main outcomes and measures:

Vessel-oriented clinical events at 2 years, a composite of cardiac death, target vessel-associated myocardial infarction, and target vessel revascularization.

Results:

This analysis included 639 patients from whom pre-PCI and post-PCI FFR values were available. Of their 837 lesions, 277 were classified into the lowest tertile (ΔFFR≤0.18), 282 into the middle tertile (0.19 ≤ ΔFFR ≤0.31), and 278 into the highest tertile (ΔFFR>0.31). Vessel-oriented clinical events were significantly more frequent in the lowest tertile (n = 25 of 277 [9.1%]) compared with the highest tertile (n = 13 of 278 [4.7%]; hazard ratio, 2.01 [95% CI, 1.03-3.92]; P = .04). In addition, a significant association was observed between ΔFFR and symptomatic relief (odds ratio, 1.33 [95% CI, 1.02-1.74]; P = .02).

Figure 2



Conclusions and relevance:

In this analysis of 2 randomized clinical trials, the larger the improvement in FFR, the larger the symptomatic relief and the lower the event rate. This suggests that measuring FFR before and after PCI provides clinically useful information.

Fournier S , Kobayashi Y, Fearon WF, Collet C, Roza da Costa B, Rioufol G, Pijls NHJ, Jüni P, De Bruyne B

Asymptomatic Patients with Abnormal Fractional Flow Reserve Treated with Medication Alone or with PCI

J Am Coll Cardiol. 2019 Sep 24;74(12):1642-1644.

Background

Asymptomatic ('silent') ischemia portends adverse outcomes.

Objectives

To investigate whether patients with hemodynamically significant stenoses but without symptoms have a worse outcome than patients with symptoms and whether PCI improve outcomes in patients with asymptomatic ischemia.

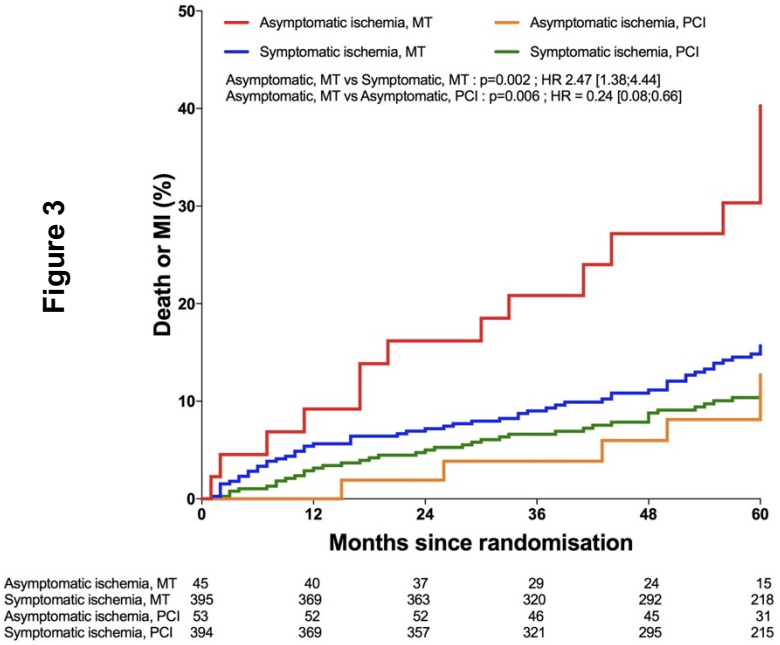
Methods

In the FAME 2 trial, we analyzed the rates of the composite of all cause death or myocardial infarction at 5 years in 887 stable patients with significant stenosis (FFR≤0.80), according to their angina class at randomization. All patients were randomly assigned to receive either Medical Therapy alone (MT group) or percutaneous coronary intervention+MT (PCI group).

Results

In the MT group, the primary composite of death or MI was significantly higher (31.1% vs. 14.4%;HR 2.47 [1.38;4.44]; p=0.002) in asymptomatic patients (n=45) than in patients with symptomatic ischemia (n=395). Conversely, their rate of non-urgent revascularization was significantly lower (17.8% vs. 37.2%;HR 0.44 [0.21;0.89]; p=0.022).

Figure 3



The rate of death or MI in asymptomatic patients was significantly lower in patients randomized to PCI as compared with patients randomized to MT alone (9.4% vs 31.1 %), with a larger benefit of PCI in asymptomatic than in symptomatic patients compared with MT alone (HR=0.24 [0.08; 0.66] versus HR=0.85 [0.58; 1.24], P for interaction=0.026).

Conclusions

In patients with significant stenoses (FFR≤0.80) but no angina, the rate of death or MI is higher than in patients with symptomatic ischemia. This difference is abolished by PCI. Symptomatic patients receiving MT alone more often cross over to PCI which may protect them from death or MI.

Milkas A, Rueda-Ochoa OL, **Fournier S**, Muller O, Van Rooij, Franco OH, Collet C, Barbato E, Kavousi M, De Bruyne B

Ten-Year Survival After FFR-Guided Strategy in Isolated Proximal Left Anterior Descending Coronary Stenosis. Matched Comparison with Normal Individuals

J Am Coll Cardiol. 2019 Sep 10;74(10):1420-1421

Aim.

To investigate the 10-year survival of patients with an isolated stenosis in the proximal left anterior descending coronary artery (LAD) in whom the treatment strategy was based on Fractional Flow Reserve (FFR) and compare their survival with a general population control group.

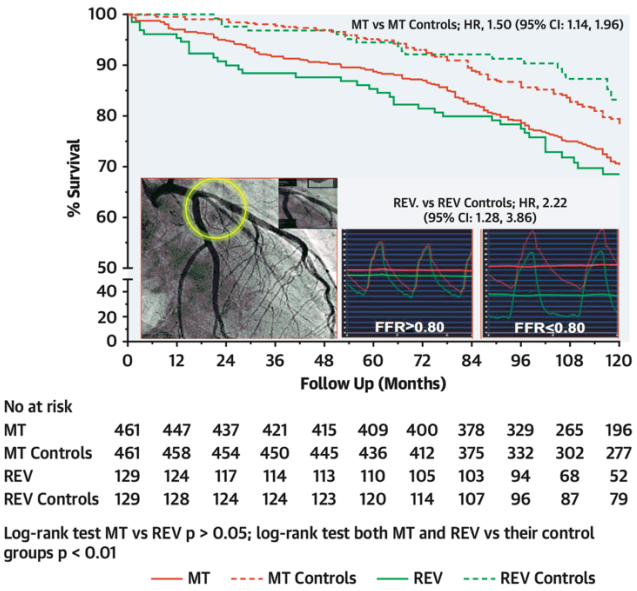
Methods.

In 729 patients with an intermediate stenosis in the proximal LAD and in whom the treatment strategy was based on FFR measurements, the rates of all-cause death, of myocardial infarction (MI), and of target vessel revascularization (TVR) were followed up during 10 years. When FFR was >0.80, medical therapy was chosen (MT group, n=564). When FFR was ≤0.80, revascularization therapy was performed (REV group, n= 165). In addition, all-cause mortality of the two patient groups was compared with two corresponding control groups from the population-based Rotterdam Study using Propensity Score Matching Greedy approach.

Results.

The follow-up was complete for all-cause mortality and was 90% and 98% complete in the MT and REV groups respectively, for MI or TVR. At 10-year, the MT and REV groups did not differ significantly for all-cause mortality (hazard ratio [HR] 0.97; 95% Confidence Interval [CI]: 0.67

Figure 4



to 1.40). In contrast, when compared to their respective control groups, all-cause mortality was significantly higher in the MT group (hazard ratio [HR] 1.64; 95% Confidence Interval [CI]: 1.24 to 2.16) and in the REV group (hazard ratio [HR] 1.83; 95% Confidence Interval [CI]: 1.83; 1.08 to 3.09).

Conclusions.

In patients with an isolated stenosis in the proximal LAD, medical therapy for FFR-negative stenoses and revascularization of FFR-positive stenoses is associated with similar survival rates. Yet, regardless of the treatment strategy, these patients have a significantly higher all-cause death than their matched controls without known CAD.

Di Gioia G; De Bruyne B, Pellicano M, Bartunek J, Colaiori , Fiordelisi A, Canciello G, Xaplanteris P, **Fournier S**, Katbeh A, Franco D; Kodeboina M, Morisco C, Van Praet F, Casselman F, Degrieck I, Stockman B, Vanderheyden M; Barbato E

Fractional Flow Reserve in patients with reduced ejection fraction

Eur Heart J . 2020 May 1;41(17):1665-1672.

Aims

Fractional flow reserve (FFR) has never been investigated in patients with reduced ejection fraction and associated coronary artery disease (CAD). We evaluated the impact of FFR on the management strategies of these patients and related outcomes.

Methods and results

From 2002 to 2010, all consecutive patients with left ventricular ejection fraction (LVEF) ≤50% undergoing coronary angiography with ≥1 intermediate coronary stenosis [diameter stenosis (DS)% 50-70%] treated based on angiography (Angiography-guided group) or according to FFR (FFR-guided group) were screened for inclusion. In the FFR-guided group, 433 patients were matched with 866 contemporary patients of the Angiography-guided group. For outcome comparison, 617 control patients with LVEF >50% were included. After FFR, stenotic vessels per patient were significantly downgraded compared with the Angiography-guided group (1.43 ± 0.98 vs. 1.97 ± 0.84; P < 0.001).

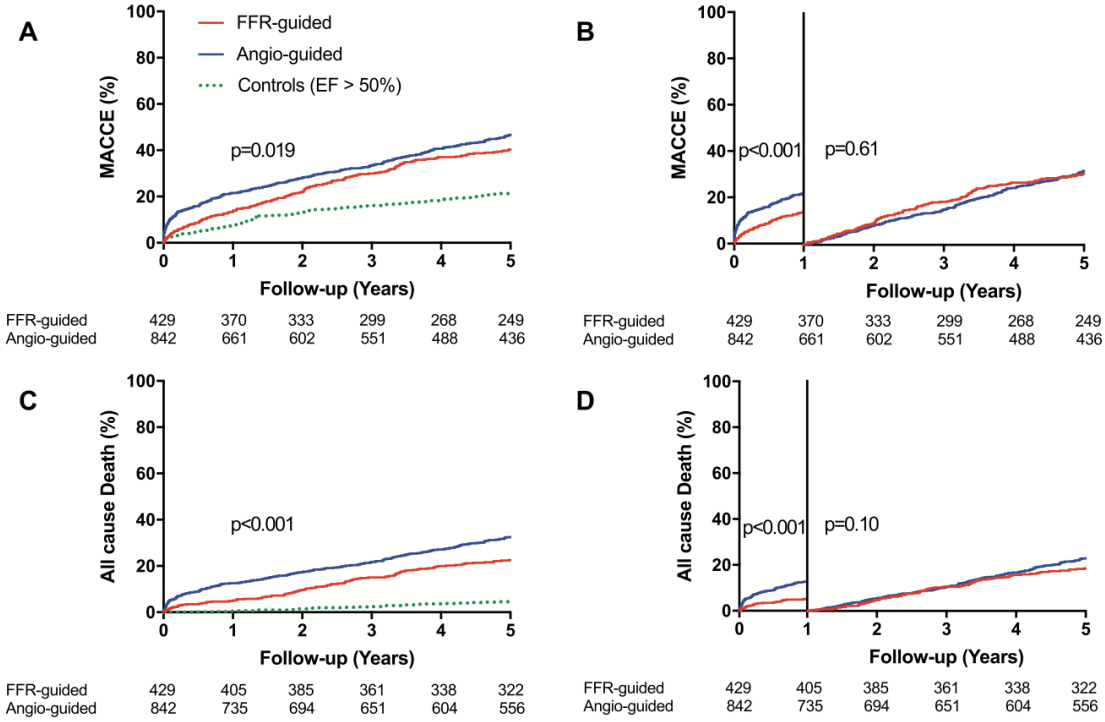


Figure 5

This was associated with lower revascularization rate (52% vs. 62%; P < 0.001) in the FFR-guided vs. the Angiography-guided group. All-cause death at 5 years of follow-up was significantly lower in the FFR-guided as compared with Angiography-guided group [22% vs. 31%. HR (95% CI) 0.64 (0.51-0.81); P < 0.001]. Similarly, rate of major adverse cardiovascular and cerebrovascular events (MACCE: composite of all-cause death, myocardial infarction, revascularization, and stroke) was significantly lower in the FFR-guided group [40% vs. 46% in the Angiography-guided group. HR (95% CI) 0.81 (0.67-0.97); P = 0.019]. Higher rates of death and MACCE were observed in patients with reduced LVEF compared with the control cohort.

Conclusions

In patients with reduced LVEF and CAD, FFR-guided revascularization was associated with lower rates of death and MACCE at 5 years as compared with the Angiography-guided strategy. This beneficial impact was observed in parallel with less coronary artery bypass grafting and more patients deferred to percutaneous coronary intervention or medical therapy.

Fournier S, Collet C, Xaplanteris P, Zimmermann FM, Toth GG, Tonino PAL, Pijls NHJ, Colaiori I, Di Gioia G, Barbato E, Jüni P, Fearon WF, De Bruyne B.

Global FFR Value Predicts 5-Year Outcomes in Patients with Coronary Atherosclerosis but Without Ischemia

J Am Heart Assoc. 2020 Dec 15;9(24):e017729.

Background

Global fractional flow reserve (FFR) - i.e. the sum of the FFR values in the three major coronary arteries - is a physiologic correlate of global atherosclerotic burden. The objective of the present study was to investigate the value of global FFR in predicting long-term clinical outcome of patients with stable coronary artery disease but no ischemia-inducing stenosis.

Methods and Results

We studied major adverse cardiac events (MACE:all-cause death, myocardial infarction and any revascularization) after 5 years in 1,122 patients without significant stenosis (all FFR>0.80,n=275) or with at least one significant stenosis successfully treated by PCI (i.e. post-PCI FFR >0.80,n=847). The patients were stratified into low, mid or high tertiles of global FFR (≤2.80; 2.80-2.88; ≥2.88).

Patients in the lowest tertile of global FFR showed the highest 5-year MACE rate compared to those in the mid or high tertile of global FFR (27.5% vs. 22.0 and 20.9%, respectively;log-rank p=0.040). The higher 5-year MACE rate was mainly driven by a higher rate of revascularization in the low global FFR group (16.4% vs. 11.3% and 11.8%, respectively, log-rank p=0.038).

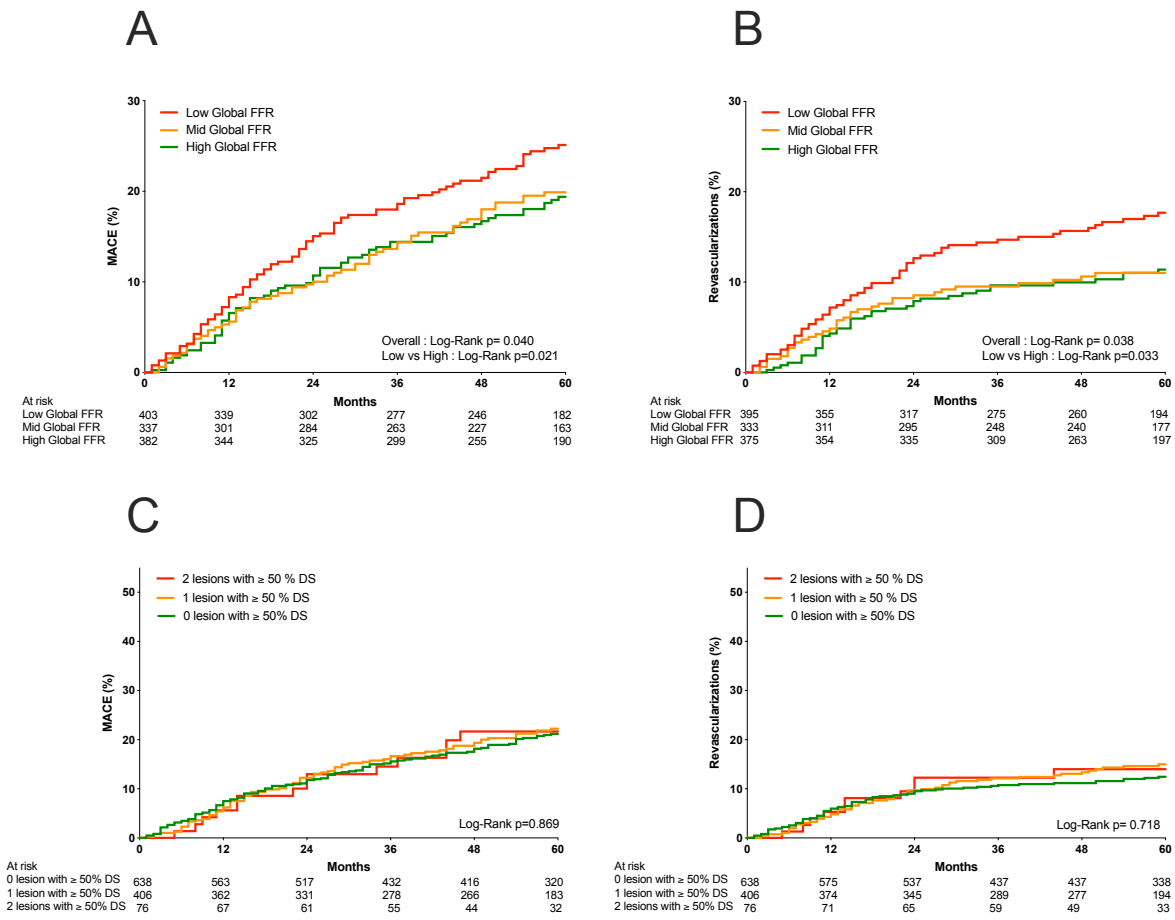


Figure 6

In a multivariable model, an increase in global FFR of 0.1 unit was associated with a significant reduction in the rates of MACE (HR=0.988, 95% CI 0.977 to 0.998; p=0.023), myocardial infarction (HR=0.982, 95% CI 0.966 to 0.998;p=0.032) and revascularization (HR=0.985, 95% CI 0.972 to 0.999];p=0.040).

Conclusions

Even in the absence of ischemia-producing stenoses, patients with a low global FFR, physiologic correlate of global atherosclerotic burden, present a higher risk of MACE at 5-year follow-up.

Toth GG, De Bruyne B, Kala P, Ribichini FL, Casselman F, Ramos R, Piroth Z, **Fournier S,** Piccoli A, Van Mieghem C, Penicka M, Mates M, Nemec P, Van Praet F, Stockman B, Degriek I, Barbato E.
Graft patency after FFR-guided versus angiography-guided coronary artery bypass grafting. The GRAFFITI trial.
EuroIntervention. 2019 Dec 6;15(11):e999-e1005

Aims: The aim of this study was to assess prospectively the clinical benefits of fractional flow reserve (FFR) in guiding coronary artery bypass grafting (CABG).

Methods and results: GRAFFITI is a single-blinded, prospective, multicentre, randomised controlled trial of FFR-guided versus angiography-guided CABG. We enrolled patients undergoing coronary angiography, having a significantly diseased left anterior descending artery or left main stem and at least one more major coronary artery with intermediate stenosis, assessed by FFR. Surgical strategy was defined based on angiography, blinded to FFR values prior to randomisation. After randomisation, patients were operated on either following the angiography-based strategy (angiography-guided group) or according to FFR, i.e., with an FFR ≤0.80 as cut-off for grafting (FFR-guided group). The primary endpoint was graft patency at 12 months.

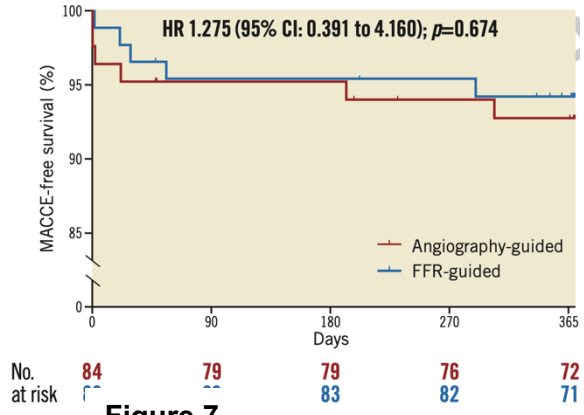


Figure 7

Between March 2012 and December 2016, 172 patients were randomised either to the angiography-guided group (84 patients) or to the FFR-guided group (88 patients). The patients had a median of three [3; 4] lesions; diameter stenosis was 65% (50%; 80%), FFR was 0.72 (0.50; 0.82). Compared to the angiography-guided group, the FFR-guided group received fewer anastomoses (3 [3; 3] vs 2 [2; 3], respectively; p=0.004). One-year angiographic follow-up showed no difference in overall graft patency (126 [80%] vs 113 [81%], respectively; p=0.885). One-year clinical follow-up, available in 98% of patients, showed no difference in the composite of death, myocardial infarction, target vessel revascularisation and stroke.

Conclusions: FFR guidance of CABG has no impact on one-year graft patency, but it is associated with a simplified surgical procedure.

Fournier S, Toth GG, De Bruyne B, Kala P, Ribichini FL, Casselman F, Ramos R, Piroth Z, Piccoli A, Penicka M, Mates M, Nemec P, Van Praet F, Stockman B, Degriek I, Pellicano M, Barbato E.

Changes in surgical revascularization strategy after fractional flow reserve.

Catheter Cardiovasc Interv . 2021 Apr 10. doi: 10.1002/ccd.29694. Online ahead of print.

Aims: In the randomized GRAFFITI trial, surgeons drew their strategy based on coronary angiography. When patients were randomized to fractional flow reserve (FFR)-guidance, surgeons were informed of the FFR values and asked to redraw their strategy. The aim of this study was to investigate the changes induced by FFR knowledge.

Methods and results: The intended and performed strategy (before and after FFR) were compared. Among 172 patients, 84 with 300 lesions were randomized to the FFR-guided group. The intended strategy was to bypass 236 stenoses:108 with a venous and 128 with an arterial graft. After disclosing FFR, a change in strategy occurred in 64 lesions (21.3%) of 48 (55%) patients. Among 64 lesions for which the intended strategy was medical therapy, 16 (25%) were bypassed after disclosing FFR. The number of procedures with >1 venous graft planned was significantly reduced from 37 to 27 patients (p = .031). The proportion of on-pump surgery was significantly reduced from 71 to 61 patients (p = .006). The rates of clinical events at 1 year were similar between patients with or without at least one change in strategy.

Discussion: FFR-guided CABG is associated with a simplified surgical procedure in 55% of the patients, with similar clinical outcomes.

Fournier S, Toth GG, Colaiori I, De Bruyne B, Barbato E

Long-term patency of coronary artery bypass graftsafter Fractional Flow Reserve guided implantation

Circ Cardiovasc Interv. 2019 May;12(5):e007712

At 6 years, 76 of 512 (15%) grafts were occluded. The proportion of occluded venous grafts was significantly higher than the proportion of occluded arterial grafts (24% versus 10%, respectively; HR=2.25 [1.43–3.55]; P value <0.001). When considering all grafts, occlusion rate was significantly lower in the FFR-guided as compared with the angiography-guided group (9% versus 17%, respectively; P value, 0.024; HR=0.49 [0.26–0.92]; Figure [A]). Likewise, among the arterial grafts, a lower occlusion rate was observed in the FFR-guided group (5% versus 12%, respectively; HR=0.33 [0.13–0.87]; P value =0.018; Figure [B]). Of importance, in

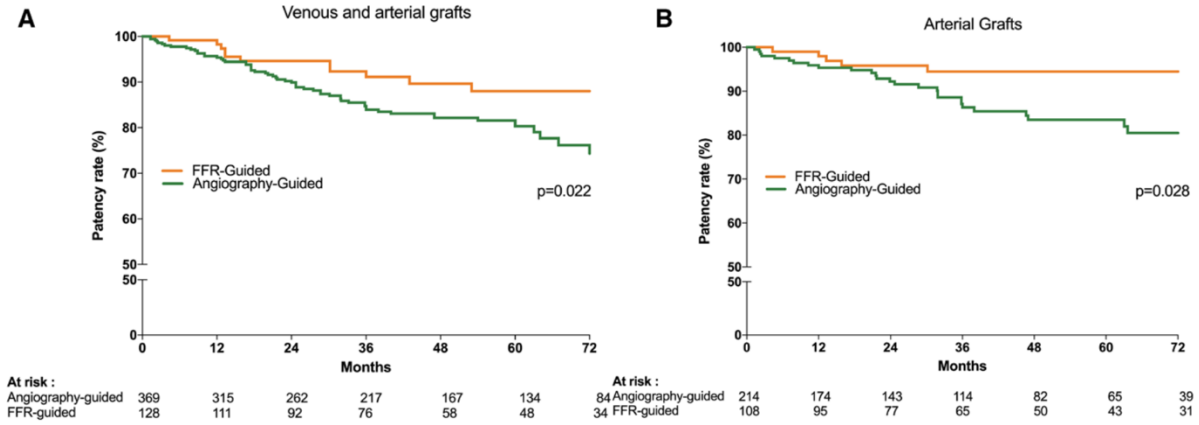


Figure 8

arterial grafts, FFR guidance was the only predictor of graft patency with a 3-fold probability of patent grafts at 6-year follow-up (HR, 2.99 [1.153–7.781]). In contrast, among venous grafts, occlusion rate was similar both in the FFR-guided and in the angiography-guided group (10% versus 14%; HR=1.61 [0.68–3.82]; P value =0.272). The P value for interaction (guidance/type of graft) was significant (P=0.017).

4. CHAPTER II : Beyond pressure : the coronary artery absolute flow

Introduction and overview of Chapter 2

While the previous Chapter was focused on FFR, this metric only reflects the contribution of epicardial stenoses to the potential decrease of the myocardial perfusion. However, the coronary blood flow essential for proper myocardial function is also influenced by the state of the microcirculation (39, 40). To investigate this latter, measurements of microvascular resistances are required. The Index of Microcirculatory Resistance (IMR) – based on manual injections of boluses of saline - has been introduced as an indirect marker (41) allowing an improved risk stratification on top of FFR among patient with intermediate coronary lesions and FFR >0.8 (42). However, IMR is an index but not a measurement tool allowing to quantify the function of the microcirculation in absolute terms. Before the beginning of my PhD, we reported a method based on continuous thermodilution allowing to obtain both absolute coronary blood flow and absolute microvascular resistance (43). Briefly, this is obtained by infusing saline (at room temperature) with a known and chosen infusion rate through a dedicated monorail catheter (Rayflow, Hexacath, Paris, France). A pressure/temperature sensor-tipped guidewire (similar to the one used to measure FFR) is then used to measure the temperature of saline as it enters the vessel, the temperature of the blood and saline mixed in the distal part of the vessel, together with the distal coronary pressure.

We used this technology (ie the ability to measure the coronary absolute flow) to demonstrate a fundamental principle of FFR: the assumption that the relationship between flow and pressure during hyperemia is linear. This principle has been described in anesthetized animals but had never been demonstrated in humans. The demonstration of this linear relationship has been demonstrated in a research letter which is included in this thesis:

- **Fournier S,** Colaiori I, Di Gioia g, Mizukami T, De Bruyne B
  Hyperemic Pressure-Flow Relationship in Man
  J Am Coll Cardiol. 2019 Mar 19;73(10):1229-1230.

To demonstrate it, immediately after a PCI of a proximal LAD stenosis, a RayFlow catheter (Hexacath, Paris, France) was advanced over a pressure/temperature sensor wire in the proximal LAD. Over the regular wire that was used for the PCI, a semi compliant balloon was advanced in the stented segment. Saline at room temperature was infused at 20 ml/min through the RayFlow catheter to measure hyperemic absolute flow. Under this steady state hyperemia, the balloon catheter was slowly inflated to obtain a graded, controlled stenosis. In this setting, we were able to demonstrate the linearity of the flow-pressure relationship in humans.

The use of this new technology based on continuous thermodilution that enables the quantification of absolute coronary blood flow and absolute microvascular resistance opens doors to new field of research, but an important prerequisite for its clinical application was the definition of normal values. This was one of the objectives of this thesis. The results presented hereafter are the abstract of the following publication:

- **Fournier S,** Keulards DCJ, van 't Veer M, Colaiori I, Di Gioia G, Zimmermann FM, Mizukami T, Nagumo S, Kodeboina M, El Farissi M, Zelis JM, Sonck J, Collet C, Pijls NHJ, De Bruyne B.
  Normal Values of Thermodilution-Derived Absolute Coronary Blood Flow and Microvascular Resistance in Humans.
  EuroIntervention. 2021 Jul 20;17(4):e309-e316.

In this study including 25 “normal patients”, thermodilution-derived hyperemic flow and total, epicardial, and microvascular absolute resistances were measured allowing us to report “normal values” for the first time.

In the early stages of the use of this technology, it appeared that intracoronary infusion of saline at room temperature at the rates of 15 to 20 mL/min through the lateral side-holes of the dedicated catheter induced hyperemia but that infusion of saline at lower rates (5 and 10 mL/min) did not. Of interest, saline infused at 20 mL/min through an end hole instead of side holes did not induce maximal hyperemia. Accordingly, it challenged us to investigate the mechanisms of this hyperemic response (in animals) and we suggested that this hyperemia might be induced by epicardial wall vibrations. The report of these investigations present in this manuscript is the abstract of the following publication:

- Adjedj J, Picard F, Collet C, Bruneval P, **Fournier S,** Bize A, Sambin L, Berdeaux A, Varenne O, De Bruyne B, Ghaleh B.
  Intracoronary Saline-Induced Hyperemia During Coronary Thermodilution Measurements of Absolute Coronary Blood Flow: An Animal Mechanistic Study.
  J Am Heart Assoc. 2020 Jul 21:e015793.

In this publication, we report the analyses based on our experiments on 20 open chest pigs where different potential mechanisms of saline-induced hyperemia were compared versus adenosine by testing various infusion rates / infusion content and temperature as well as NO production inhibition with L-arginine methyl ester and endothelial denudation or also effects of vibrations generated by rotational atherectomy. These different investigations showed us that vasodilation is related neither to the composition/temperature of the indicator nor is it endothelial mediated but that it could be elicited by epicardial wall vibrations.

These different investigations showed us that the infusion of saline at room temperature allowed us to measure accurately coronary flow during hyperemia, but we also decided to test the method to investigate whether continuous coronary thermodilution using lower infusion

rates also enables coronary blood flow measurements at rest. The report of these investigations present in this manuscript is the abstract of the following publication:

- Thermodilution-Derived Volumetric Resting Coronary Blood Flow Measurement in Humans.
  Gallinoro E, Candreva A, Colaiori I, Kodeboina M, **Fournier S,** Nelis O, Di Gioia G, Sonck J, van 't Veer M, Pijls NHJ, Collet C, De Bruyne B.
  EuroIntervention. 2021 Feb 2:EIJ-D-20-01092. doi: 10.4244/EIJ-D-20-01092
  Online ahead of print.PMID: 33528358

In this study, we observed - as compared to baseline - that saline infusion at 10 mL/min did not change Pd/Pa (no hyperemia) but that stable thermodilution tracings were obtained. Thus, continuous thermodilution can quantify absolute resting coronary blood flow and therefore, it can be also be used to calculate coronary flow reserve and microvascular resistance reserve.

While the first step in the introduction of a new method is the demonstration of its safety and of its reproducibility, we tried to confirm its excellent accuracy using it in the specific context of coronary bifurcations where the flow in the main artery equals the sum of the flows in the 2 daughter arteries. The report of these investigations present in this manuscript is the abstract of the following publication:

- Candreva A, Gallinoro E, **Fournier S**, Izaga E, Finet G, De Bruyne B, Gutiérrez-Barrios A.
  Absolute Blood Flow in the Left Main Coronary Artery and Its Distribution.
  JACC Cardiovasc Interv. 2021 Feb 22;14(4):482-484.

Using the left main coronary artery (LMCA) as well as the Left Anterior Descending (LAD) and Circumflex (LCX) coronary arteries, we measured the flow in these 3 vessels and by reporting that QLMCA = QLAD + QLCx, we confirmed the accuracy of thermodilution-derived flow measurements and its application in the LMCA.

As the flow in a coronary artery is closely linked to the myocardial mass depending on this coronary artery, the calculation of myocardial mass at risk when a coronary stenosis is seen on a CT would be an extremely interesting perspective, especially in the era of FFR-CT where fluid dynamic is computed. Accordingly, we conducted a study in which our aim was to compare relative territorial-based CTmass assessment with relative flow distribution. Its results presented here come from the abstract of the following publication:

- Keulards DCJ*, **Fournier S***, van 't Veer M, Colaiori I, Zelis JM, El Farissi M, Zimmermann FM, Collet C, De Bruyne B, Pijls NHJ
  Computed tomographic myocardial mass compared with invasive myocardial perfusion measurement.
  Heart . 2020 Oct;106(19):1489-1494.
  * equally contributed

In this study based on 35 patients with (near) normal coronary arteries who also underwent a cardiac CT to calculate the myocardial mass and who then underwent flow measurement in all 3 major coronary arteries by continuous thermodilution, mass and flows were calculated as relative percentages of total mass and perfusion. We observed an intraclass correlation between the two techniques of 0.90 and accordingly, we demonstrated the existence of a close relationship between the relative mass of the perfusion territory calculated by the specific CT algorithm and invasively measured myocardial perfusion.

Finally, given the rapid development of this technology and the reliability of the measurements, we wrote a State-of-the-Art Review whose abstract is presented in the manuscript:

- Candreva A, Gallinoro E, van 't Veer M, Sonck J, Collet C, Di Gioia G, Kodeboina M, Mizukami T, Nagumo S, Keulards D, **Fournier S,** Pijls NHJ, De Bruyne B.
  Basics of Coronary Thermodilution.
  JACC Cardiovasc Interv. 2021 Mar 22;14(6):595-605.

Fournier S, Colaiori I, Di Gioia g, Mizukami T, De Bruyne B

Hyperemic Pressure-Flow Relationship in Man

J Am Coll Cardiol. 2019 Mar 19;73(10):1229-1230.

Fractional flow reserve (FFR) represents the ratio of hyperemic flow in the presence of an epicardial stenosis to hyperemic flow in the hypothetical absence of this stenosis. FFR can be calculated from hyperemic pressure measurements, provided the relationship between flow and pressure during hyperemia is linear. This linearity, which constitutes the cornerstone of the concept, has been described in anesthetized open-chest dogs but has never been demonstrated in humans. The relationship between coronary flow and coronary driving pressure during maximal microvascular vasodilation was investigated in 1 patient immediately upon percutaneous coronary intervention (PCI).

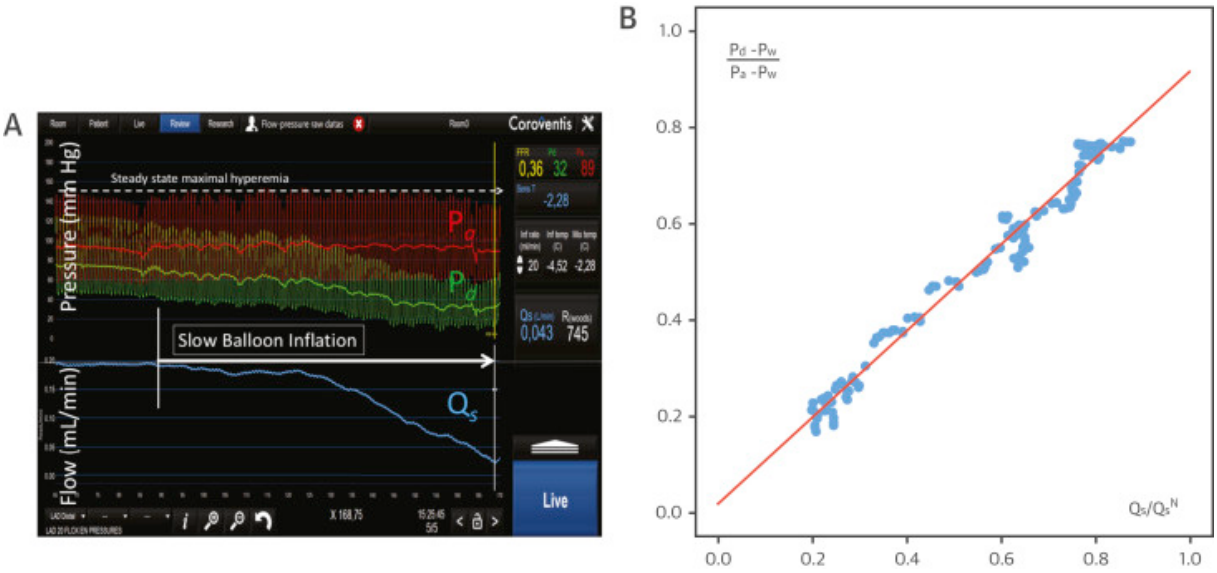


Figure 9

Fournier S, Keulards DCJ, van 't Veer M, Colaiori I, Di Gioia G, Zimmermann FM, Mizukami T, Nagumo S, Kodeboina M, El Farissi M, Zelis JM, Sonck J, Collet C, Pijls NHJ, De Bruyne B.

Normal Values of Thermodilution-Derived Absolute Coronary Blood Flow and Microvascular Resistance in Humans.

EuroIntervention . 2021 Jul 20;17(4):e309-e316.

Aims: Absolute hyperemic coronary blood flow (Q, in mL/min) and resistance (R, in Woods Units, WU) can be measured invasively by continuous thermodilution. The aim of this study was to assess normal reference values of Q and R.

Methods and results: In 177 arteries (69 patients: 25 controls i.e. without identifiable coronary atherosclerosis; 44 patients with mild, non-obstructive atherosclerosis), thermodilution-derived hyperemic Q and total, epicardial, and microvascular absolute resistances (Rtot, Repi, and Rmicro) were measured. In 20 controls and 29 patients measurements were obtained in all 3 major coronary arteries,thus allowing calculations of Q and R for the whole heart. In 15 controls (41 vessels) and 25 patients (71 vessels),vessel-specific myocardial mass was derived from coronary computed tomography angiography. Whole heart hyperemic Q tended to be higher in controls compared to patients (668±185 vs 582±138 mL/min,p=0.068). In the left anterior descending coronary artery (LAD), hyperemic Q was significantly higher (293±102 mL/min versus 228±71 mL/min,p=0.004) in controls than in patients . This was mainly driven by a difference in Repi (43±23 vs 83±41 WU, p=0.048),without significant differences in Rmicro. After adjustment for vessels-specific myocardial mass, hyperemic Q was similar in the 3 vascular territories (5.9±1.9,4.9±1.7,and 5.3±2.1 mL/min/g,p=0.44,in the LAD, left circumflex and right coronary artery,respectively).

Conclusions: The present report provides reference values of absolute coronary hyperemic Q and R. Q was homogeneously distributed in the 3 major myocardial territories but the large ranges of observed hyperemic values of flow and and of microvascular resistance preclude their clinical use for interpatient comparison.

Adjedj J, Picard F, Collet C, Bruneval P, **Fournier S**, Bize A, Sambin L, Berdeaux A, Varenne O, De Bruyne B, Ghaleh B.
Intracoronary Saline-Induced Hyperemia During Coronary Thermodilution Measurements of Absolute Coronary Blood Flow: An Animal Mechanistic Study.
J Am Heart Assoc. 2020 Jul 21:e015793.

Background

Absolute hyperemic coronary blood flow and microvascular resistances can be measured by continuous thermodilution with a dedicated infusion catheter. We aimed to determine the mechanisms of this hyperemic response in animal.

Methods and Results

Twenty open chest pigs were instrumented with flow probes on coronary arteries. The following possible mechanisms of saline-induced hyperemia were explored compared with maximal hyperemia achieve with adenosine by testing: (1) various infusion rates; (2) various infusion content and temperature; (3) NO production inhibition with L-arginine methyl ester and endothelial denudation; (4) effects of vibrations generated by rotational atherectomy and of infusion through one end-hole versus side-holes. Saline infusion rates of 5, 10 and 15 mL/min did not reach maximal hyperemia as compared with adenosine. Percentage of coronary blood flow expressed in percent of the coronary blood flow after adenosine were 48±17% at baseline,

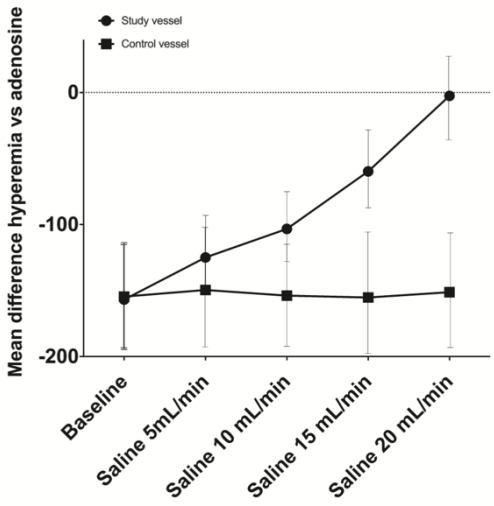


Figure 10

57±18% at 5 mL/min, 65±17% at 10 mL/min, 82±26% at 15 mL/min and 107±18% at 20 mL/min.

Maximal hyperemia was observed during infusion of both saline at body temperature and glucose 5%, after endothelial denudation, l-arginine methyl ester administration, and after stent implantation. The activation of a Rota burr in the first millimeters of the epicardial artery also induced maximal hyperemia. Maximal hyperemia was achieved by infusion through lateral side-holes but not through an end-hole catheter.

Conclusions

Infusion of saline at 20 mL/min through a catheter with side holes in the first millimeters of the epicardial artery induces maximal hyperemia. The data indicate that this vasodilation is related neither to the composition/temperature of the indicator nor is it endothelial mediated. It is suggested that it could be elicited by epicardial wall vibrations.

Gallinoro E, Candreva A, Colaiori I, Kodeboina M, **Fournier S**, Nelis O, Di Gioia G, Sonck J, van 't Veer M, Pijls NHJ, Collet C, De Bruyne B.
Thermodilution-Derived Volumetric Resting Coronary Blood Flow Measurement in Humans.
EuroIntervention. 2021 Feb 2:EIJ-D-20-01092. doi: 10.4244/EIJ-D-20-01092. Online ahead of print.

Background: Quantification of microvascular function requires the measurement of flow and resistance at rest and during hyperemia. Continuous intracoronary thermodilution accurately measures coronary flow during hyperemia.

Aims: To study whether continuous coronary thermodilution using lower infusion rates also enables volumetric coronary blood flow measurements (in mL/min) at rest.

Methods: In 59 patients (88 arteries), the ratio of distal to proximal coronary pressure (Pd/Pa), as well as absolute blood flow (in mL/min) by continuous thermodilution, were recorded using a pressure/temperature guide wire. Saline was infused at rates of 10 and 20 mL/min. In 27 arteries, Doppler average peak velocity (APV) was measured simultaneously. Pd/Pa, APV, thermodilution-derived coronary flow reserve (CFRthermo) and coronary flow velocity reserve (CFVR) were assessed. In 10 arteries, simultaneous recordings were obtained at saline infusion rates of 6, 8, 10 and 20 mL/min.

Results: Compared to baseline, saline infusion at 10 mL/min did not change Pd/Pa (0.95±0.05 versus 0.94±0.05, p=0.49) nor APV (22±8 versus 23±8 cm/s, p=0.60); conversely, an infusion rate of 20 mL/min induced a decrease in Pd/Pa and an increase in APV. Stable thermodilution tracings were obtained during saline infusion at 8 and 10 mL/min, but not at 6 mL/min. Mean values of CFRthermo and CFVR were similar (2.78±0.91 versus 2.76±1.06, p=0.935) and their individual values correlated closely (r=0.89, 95%CI 0.78 - 0.95, p<0.001).

Conclusions: In addition to hyperemic flow, continuous thermodilution can quantify absolute resting coronary blood flow; therefore it can be used to calculate coronary flow reserve and microvascular resistance reserve.

Candreva A, Gallinoro E, **Fournier S**, Izaga E, Finet G, De Bruyne B, Gutiérrez-Barrios A

Absolute Blood Flow in the Left Main Coronary Artery and Its Distribution.

JACC Cardiovasc Interv. 2021 Feb 22;14(4):482-484.

Twenty patients (mean age 70 ± 13 years, 30% female, 85% with angina) were analyzed. Mean measured flows were 261 ± 108 (range from 105 to 540) ml/min, 183 ± 67 (range 72 to 339) ml/min, and 443 ± 117 (range 213 to 718) ml/min in the LAD, LCX, and LMCA, respectively. The sum of QLAD and QLCx (444 ± 124 ml/min; p = 0.87) correlated well with QLMCA (Pearson's r = 0.94; Passing-Bablok intercept = −28.2 [95% confidence interval: −109.2 to 27.4] and slope = 1.06 [95% confidence interval: 0.94 to 1.21] (**Figure**). Likewise, the Bland-Altman analysis showed a good agreement (mean bias −1.45) with a moderate spread (SD = ±41.03).

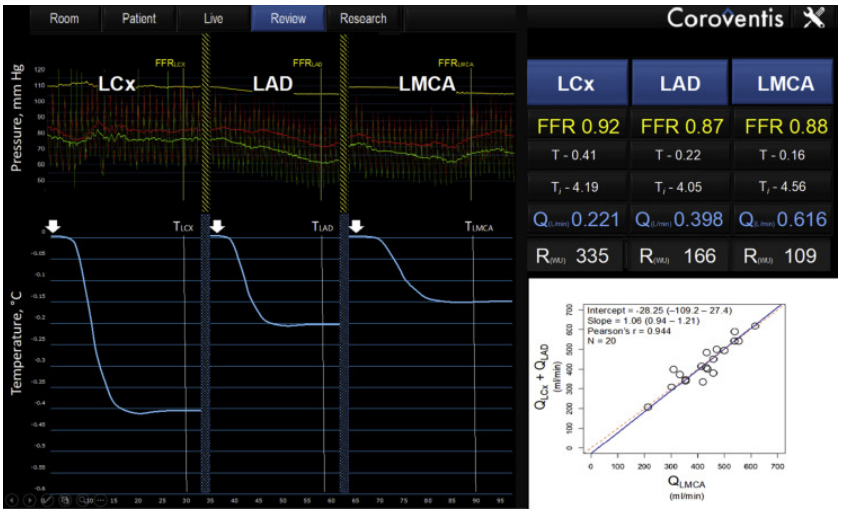


Figure 11

Our study confirmed the law of conservation of flow during hyperemia, such that QLMCA = QLAD + QLCx. At the same time, this close correlation confirmed the accuracy of thermodilution-derived flow measurements and validated its application in the LMCA. It is important to note that the flow measured is the one at the level of the side holes of the infusion catheter, and not at the level of the temperature sensor.

Keulards DCJ*, **Fournier S***, van 't Veer M, Colaiori I, Zelis JM, El Farissi M, Zimmermann FM, Collet C, De Bruyne B, Pijls NHJ

Computed tomographic myocardial mass compared with invasive myocardial perfusion measurement.

Heart . 2020 Oct;106(19):1489-1494.

* equally contributed

Objective:

The prognostic importance of a coronary stenosis depends on its functional severity and its depending myocardial mass. Functional severity can be assessed by fractional flow reserve (FFR), estimated non-invasively by a specific validated CT algorithm (FFR_{CT}). Calculation of myocardial mass at risk by that same set of CT data (CTmass), however, has not been prospectively validated so far. The aim of the present study was to compare relative territorial-based CTmass assessment with relative flow distribution, which is closely linked to true myocardial mass.

Methods:

In this exploratory study, 35 patients with (near) normal coronary arteries underwent CT scanning for computed flow-based CTmass assessment and underwent invasive myocardial perfusion measurement in all 3 major coronary arteries by continuous thermodilution. Next, the mass and flows were calculated as relative percentages of total mass and perfusion.

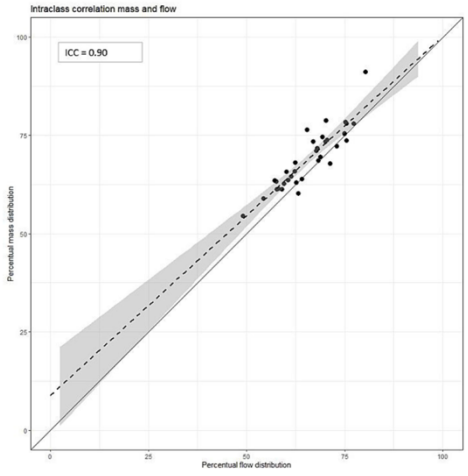


Figure 12

Results

The mean difference between CTmass per territory and invasively measured myocardial perfusion, both expressed as percentage of total mass and perfusion, was 5.3±6.2% for the left anterior descending territory, -2.0±7.4% for the left circumflex territory and -3.2±3.4% for the right coronary artery territory. The intraclass correlation between the two techniques was 0.90.

Conclusions

Our study shows a close relationship between the relative mass of the perfusion territory calculated by the specific CT algorithm and invasively measured myocardial perfusion. As such, these data support the use of CTmass to estimate territorial myocardium-at-risk in proximal coronary arteries.

Candreva A, Gallinoro E, van 't Veer M, Sonck J, Collet C, Di Gioia G, Kodeboina M, Mizukami T, Nagumo S, Keulards D, **Fournier S**, Pijls NHJ, De Bruyne B.
Basics of Coronary Thermodilution.
JACC Cardiovasc Interv. 2021 Mar 22;14(6):595-605.

Coronary microvascular dysfunction is a highly prevalent condition in both obstructive and nonobstructive coronary artery disease. Intracoronary thermodilution is a promising technique to investigate coronary microvascular (dys)function in vivo and to assess its most important metric: microvascular resistance. Here, the authors provide a practical review of bolus and continuous thermodilution for the measurement of coronary flow and microvascular resistance. The authors describe the basic principles of indicator-dilution theory and of coronary thermodilution and detail the practicalities of their application in the catheterization laboratory. Finally, the authors discuss contemporary clinical applications of coronary thermodilution-based microvascular assessment in humans and future perspectives.

5. CHAPTER III : Beyond the wire : angiography-Derived FFR

Introduction and overview of Chapter 3

In the Chapter I, the better clinical outcomes of patients in whom fractional flow reserve (FFR) was measured to guide revascularization were illustrated by different studies (1, 28). However, despite its numerous advantages and its recommendations in the clinical guidelines, FFR remains underused (44). Different reasons are often cited (18) such as the time required to measure an FFR, the cost of the wire, the potential technical challenges (tortuous anatomy for example), the small risk associated with maneuvering a pressure wire down a coronary artery, the multiplicity of these challenges to assess multiple vessels, some potential technical issues (drift) or even potential side effects with hyperemic agents. For these different limitations, techniques for calculating FFR without the need of a pressure wire or hyperemic agent but based on images obtained during an invasive coronary angiography have been developed. During this thesis, several works were made with this technology and using 2 different software: QFR from MEDIS and FFR_{angio} from Cathworks.

The first challenge of these new software was of course their accuracy as compared to the invasive gold standard (FFR). During this thesis, we have been involved in the FAST-FFR trial comparing FFR_{angio} versus invasive FFR (comparison of QFR with invasive FFR having already being done (45)). The results presented in this manuscript are the abstract of the following publication:

- Fearon WF, Achenbach S , Engstrom T , Assali A, Shlofmitz R , Jeremias A , **Fournier S** , Kirtane AJ, Kornowski R , Greenberg G , Jubeh R , Kolansky DM , McAndrew T , Dressler O, Maehara A , Matsumura M , Leon MB , De Bruyne B Accuracy of Fractional Flow Reserve Derived From Coronary Angiography Circulation. 2019 Jan 22;139(4):477-484.

In this trial based on 301 subjects and 319 vessels, the per-vessel sensitivity and specificity were 94% (95% CI, 88% to 97%) and 91% (86% to 95%), respectively. The diagnostic accuracy of FFR_{angio} was 92%.

Of interest, the performance of FFR_{angio} and QFR were compared in a meta-analysis which concluded that computational approaches and software packages did not influence the diagnostic accuracy of angiography-derived FFR (46).

As this trial demonstrated an excellent accuracy, we went on with the comparisons using FFR_{angio} but this time, we compared its accuracy versus the different invasive non-hyperemic pressure ratios (NHPRs). The results presented in this manuscript are based on the following publication:

- Johnson NP, Mahaera A, Achenbach S, Engstrom T, Assali A, Jeremias A, **Fournier S,** De Bruyne B, Leon MB, Fearon WF,
  Angiography-derived fractional flow reserve versus invasive non-hyperemic pressure ratios
  J Am Coll Cardiol. 2019 Jun 25;73(24):3232-3233.

In this study also based on the FAST-FFR trial, the accuracy against invasive FFR ≤0.80 was 92.4% for FFR_{angio}, 85.3% for Pd/Pa, and 82.7% for iFR and dPR. Furtheremore, FFR_{angio} agrees more often with invasive FFR than any of 3 NHPRs.

Finally, to end up with these comparisons, we also analyzed the diagnostic performance of FFR_{angio} versus FFR in various subgroups of patients. The results presented in this manuscript are the abstract of the following publication :

- Kobayashi Y, Collet C, Achenbach S, Engstrøm T, Assali A, Shlofmitz RA, **Fournier S**, Kirtane AJ, Ali ZA, Kornowski R, Leon MB, De Bruyne B, Fearon WF
  Diagnostic performance of angiography-based fractional flow reserve by patient and lesion characteristics
  EuroIntervention. 2020 May 4:EIJ-D-19-00933.

In this other FAST-FFR sub study, we investigated the diagnostic performance of FFR_{angio} in specific patient or lesion characteristics such as high body mass index, presentation with an acute coronary syndrome, or lesion location. We concluded that FFR_{angio} keeps a high diagnostic performance regardless these different situations.

The validations of these new tools having been made in the context of patients with stable coronary artery disease with epicardial stenoses, time came to investigate them in different context such as post-PCI. This was done using the angiograms of the DOCTORS trial. In this trial, 240 patients with non-ST-segment elevation acute coronary syndromes were randomized to OCT-guided PCI or to fluoroscopy-guided and the primary end point was the functional result of PCI assessed by the measure of post PCI FFR. This latter measure what used for our study:

- Rubimbura V, Guillon B, **Fournier S**, Amabile N, Chi Pan C, Combaret N, Eeckhout E, Kibler M, Silvain J, Wijns W, Schiele F, Muller O, Meneveau N, Adjedj J.
  Quantitative flow ratio virtual stenting and post stenting correlations to post stenting fractional flow reserve measurements from the DOCTORS (Does Optical Coherence Tomography Optimize Results of Stenting) study population.
  Catheter Cardiovasc Interv. 2020 Nov;96(6):1145-1153.

In this study, we analyzed post-PCI QFR from the angiographies of DOCTOR and compared them to the post-PCI FFR values. We observed that the correlation coefficient between post-

PCI FFR and post-PCI QFR was 0.79 (95% CI: 0.70–0.86). A Bland Altman analysis showed a bias of 0.01 ± 0.03 with 95% limits of agreement of −0.06 to 0.08.

Finally, we also used this technology (QFR) in a totally different way as we aimed to characterize the hemodynamic impact of mild coronary artery disease using QFR in a population of patients with only non-significant CAD at baseline that subsequently experienced a myocardial infarction in order to see if coronary stenoses that are subsequently responsible for a myocardial infarction exhibit lower QFR years before. The results presented in this manuscript are the abstract of the following publication :

- Future culprit detection based on angiography-derived FFR.
  Pagnoni M, Meier D, Candreva A, Maillard L, Adjedj J, Collet C, Mahendiran T, Cook S, Mujcinovic A, Dupré M, Rubimbura V, Roguelov C, Eeckhout E, De Bruyne B, Muller O, **Fournier S.**
  Catheter Cardiovasc Interv. 2021 Apr 29. doi: 10.1002/ccd.29736. Online ahead of print

In this pilot study, future culprit lesions (FCL) had lower QFR values than non-future culprit lesions (NCL). Of interest, in lesions with an interval < 2 years between baseline angiography and myocardial infarction, the difference in QFR was more pronounced compared to the lesions with a longer interval (FCL: 0.92 [0.85; 0.97] vs. NCL: 0.98 [0.94; 1.00], p < .001 and FCL: 0.96 [0.88; 1.00] vs. NCL: 0.98 [0.96;1.00], p = .006 respectively).

Fearon WF, Achenbach S , Engstrom T , Assali A, Shlofmitz R , Jeremias A , **Fournier S** , Kirtane AJ, Kornowski R , Greenberg G , Jubeh R , Kolansky DM , McAndrew T , Dressler O, Maehara A , Matsumura M , Leon MB , De Bruyne B

Accuracy of Fractional Flow Reserve Derived From Coronary Angiography

Circulation. 2019 Jan 22;139(4):477-484.

Background: Measuring fractional flow reserve (FFR) with a pressure wire remains underutilized because of the invasiveness of guide wire placement or the need for a hyperemic stimulus. FFR derived from routine coronary angiography (FFR_{angio}) eliminates both of these requirements and displays FFR values of the entire coronary tree. The FFR_{angio} Accuracy versus Standard FFR (FAST-FFR) study is a prospective, multicenter, international trial with the primary goal of determining the accuracy of FFR_{angio}.

Methods: Coronary angiography was performed in a routine fashion in patients with suspected coronary artery disease. FFR was measured in vessels with coronary lesions of varying severity using a coronary pressure wire and hyperemic stimulus. Based on angiograms of the respective arteries acquired in ≥2 different projections, on-site operators blinded to FFR then calculated FFR_{angio} using proprietary software. Coprimary end points were the sensitivity and specificity of the dichotomously scored FFR_{angio} for predicting pressure wire-derived FFR using a cutoff value of 0.80. The study was powered to meet prespecified performance goals for sensitivity and specificity.

Results: Ten centers in the United States, Europe, and Israel enrolled a total of 301 subjects and 319 vessels meeting inclusion/exclusion criteria which were included in the final analysis. The mean FFR was 0.81 and 43% of vessels had an FFR≤0.80. The per-vessel sensitivity and specificity were 94% (95% CI, 88% to 97%) and 91% (86% to 95%), respectively, both of which exceeded the prespecified performance goals. The diagnostic accuracy of FFR_{angio} was 92%

overall and remained high when only considering FFR values between 0.75 to 0.85 (87%). FFR_{angio} values correlated well with FFR measurements (r=0.80, P<0.001) and the Bland-Altman 95% confidence limits were between -0.14 and 0.12. The device success rate for FFR_{angio} was 99%.

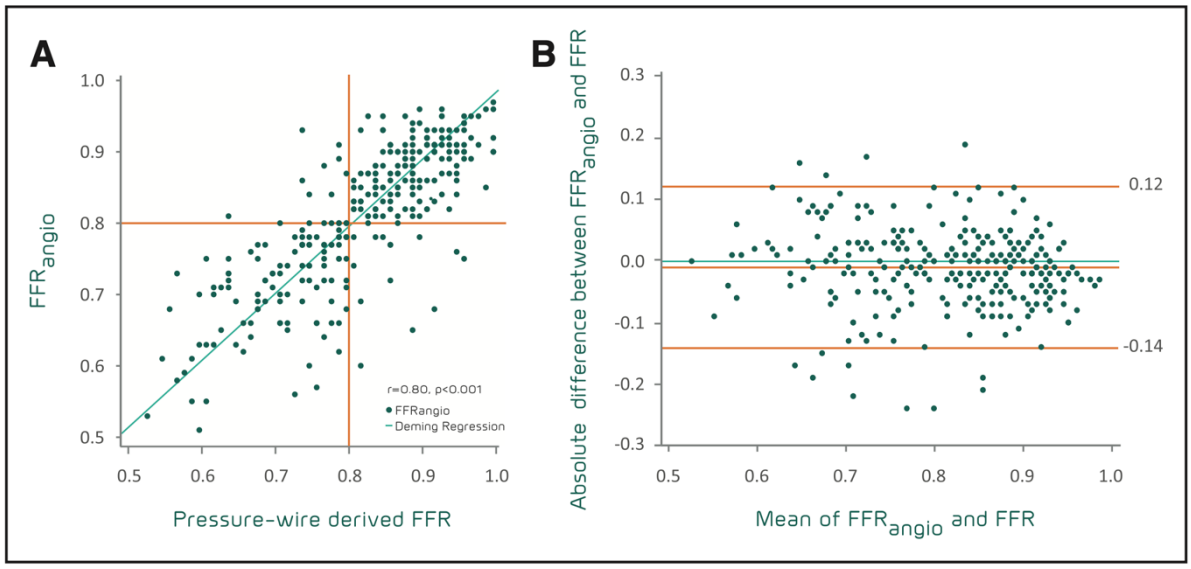


Figure 13

Conclusions: FFR_{angio} measured from the coronary angiogram alone has a high sensitivity, specificity, and accuracy compared with pressure wire-derived FFR. FFR_{angio} has the promise to substantially increase physiological coronary lesion assessment in the catheterization laboratory, thereby potentially leading to improved patient outcomes.

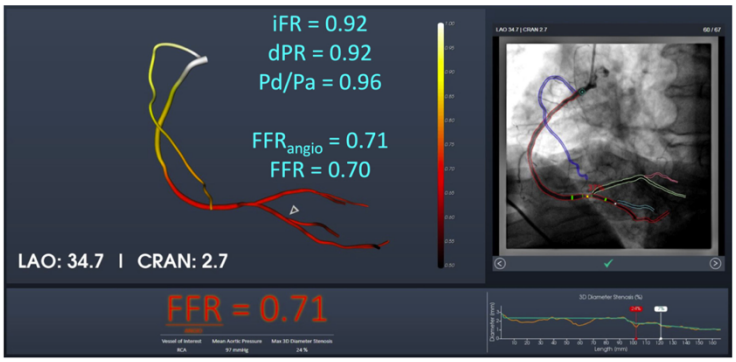
Johnson NP, Mahaera A, Achenbach S, Engstrom T, Assali A, Jeremias A, **Fournier S**, De Bruyne B, Leon MB, Fearon WF,

Angiography-derived fractional flow reserve versus invasive non-hyperemic pressure ratios

J Am Coll Cardiol. 2019 Jun 25;73(24):3232-3233.

Binary accuracy against invasive FFR ≤0.80 was 92.4% for FFRangio, 85.3% for Pd/Pa, and 82.7% for iFR and dPR. Figure 1 provides an example showing an angiogram plus all physiology indexes. In all pairwise comparisons FFRangio demonstrated superior agreement: ratio of disagreements favoring FFRangio to disagreements favoring Pd/Pa was 2.4 (in 223 cases both FFRangio and Pd/Pa agreed with FFR, in 7 cases both FFRangio and Pd/Pa disagreed with FFR, in 34 cases FFRangio agreed with FFR but Pd/Pa disagreed with FFR, and in 14 cases Pd/Pa agreed with FFR but FFRangio disagreed with FFR, so the ratio equals 34/14 = 2.4; p = 0.006); and ratio of 2.8 (p < 0.001) versus both iFR and dPR. No difference existed among the different NHPRs for predicting invasive FFR ≤0.80: ratio 2.4 (p = 0.14) for Pd/Pa versus iFR; ratio 2.8 (p = 0.12) for Pd/Pa versus dPR; and ratio 1.0 (p = 1.0) for iFR versus dPR. No significant heterogeneity of FFRangio superiority existed for lesion location (left anterior descending vs. other) or clinical presentation (stable vs. acute). Additionally, these findings did not change materially after randomly selecting a single lesion from subjects who underwent multivessel assessment.

Figure 14



Kobayashi Y, Collet C, Achenbach S, Engstrøm T, Assali A, Shlofmitz RA, **Fournier S**, Kirtane AJ, Ali ZA, Kornowski R, Leon MB, De Bruyne B, Fearon WF

Diagnostic performance of angiography-based fractional flow reserve by patient and lesion characteristics

EuroIntervention. 2020 May 4:EIJ-D-19-00933.

Aims: A large, prospective, multicenter trial recently showed that fractional flow reserve (FFR) derived from coronary angiography (FFRangio) has an accuracy of 92% compared with conventional guide-wire based FFR (FFRwire); however, little is known whether specific patient/lesion characteristics affect the diagnostic performance.

Methods and results: FFRangio was measured in a blinded fashion in 301 patients (319 vessels) who were undergoing FFRwire assessment. Using an FFRwire ≤0.80 as a reference, the diagnostic performance of FFRangio was compared in pre-specified subgroups. The mean FFRwire and FFRangio were 0.81 ± 0.13 and 0.80 ± 0.12. Overall, FFRangio had a sensitivity of 93.5% and specificity of 91.2% for predicting FFRwire. Patient characteristics including age, sex, clinical presentation, body mass index, and diabetes did not affect sensitivity or specificity (p>0.05 for all). Similarly, lesion characteristics including calcification, tortuosity did not affect sensitivity or specificity (p>0.05 for all), nor did lesion location (proximal, middle, versus distal). Sensitivity was equally high across all target vessels, while specificity was highest in the LAD and lower (~85%) in the RCA and LCx (p<0.05).

Conclusions: FFRangio derived from coronary angiography has a high diagnostic performance regardless of patient and most lesion characteristics. The interaction of vessel on the specificity will need to be confirmed in larger cohorts.

Rubimbura V, Guillon B, **Fournier S**, Amabile N, Chi Pan C, Combaret N, Eeckhout E, Kibler M, Silvain J, Wijns W, Schiele F, Muller O, Meneveau N, Adjedj J.

Quantitative flow ratio virtual stenting and post stenting correlations to post stenting fractional flow reserve measurements from the DOCTORS (Does Optical Coherence Tomography Optimize Results of Stenting) study population.

Catheter Cardiovasc Interv . 2020 Nov;96(6):1145-1153.

Objective: We sought to evaluate the correlations of pre-PCI QFR analysis with virtual PCI called residual QFR and post-PCI QFR compared to post-PCI FFR.

Background: Quantitative flow ratio (QFR) is a computation of fractional flow reserve (FFR) based on angiography without use of a pressure wire. The ability to evaluate post-PCI FFR using pre-PCI QFR analysis with a virtual PCI and the correlation between post-PCI QFR compared to post-PCI FFR remains unknown.

Methods: From the DOCTORS (Does Optical Coherence Tomography Optimize Results of Stenting) study population, we blindly analyzed residual QFR and post-PCI QFR from angiographies and compared them to post-PCI FFR.

Results: Ninety-three post-PCI QFR measurements and 84 pre-PCI residual QFR measurements were compared to post-PCI FFR measurements. No significant difference were observed between mean post-PCI FFR value (0.92 ± 0.05) compared to mean residual (0.93 ± 0.05) QFR and between mean post-PCI FFR value compared to mean post-PCI QFR values were (0.93 ± 0.05) ($p > .05$ for both). The correlation coefficient of residual QFR with

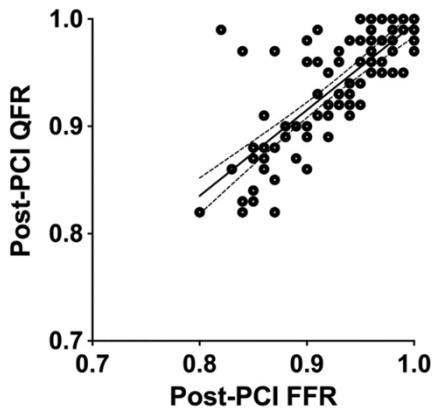


Figure 15

post-PCI FFR was 0.68 (95% CI: 0.53-0.78) and the correlation coefficient of post-PCI-QFR with post-PCI FFR was 0.79 (95% CI: 0.70-0.86).

Conclusions: Residual QFR corresponding to pre-PCI QFR analysis with virtual PCI, and post-PCI QFR analysis, correlated well with post-PCI FFR. Further studies are needed to prospectively validate a QFR-guided PCI strategy.

Pagnoni M, Meier D, Candreva A, Maillard L, Adjedj J, Collet C, Mahendiran T, Cook S, Mujcinovic A, Dupré M, Rubimbura V, Roguelov C, Eeckhout E, De Bruyne B, Muller O, **Fournier S.**

Future culprit detection based on angiography-derived FFR.

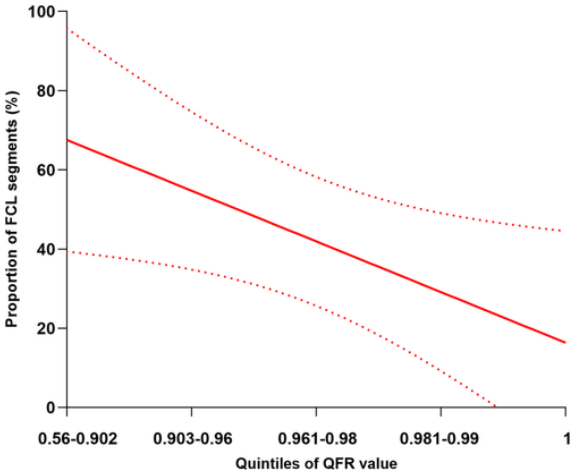
Catheter Cardiovasc Interv. 2021 Apr 29. doi: 10.1002/ccd.29736. Online ahead of print.PMID: 33913606

Objectives: We sought to characterize the hemodynamic impact of mild coronary artery disease (CAD) using quantitative flow ratio (QFR, an angiography-derived fractional flow reserve [FFR]) in a population of patients with only non-significant CAD at baseline that subsequently experienced a myocardial infarction (MI).

Background: The discriminatory value of FFR in patients with mild CAD remains imperfect.

Methods: We retrospectively included patients who underwent invasive coronary angiography for an MI, in whom another angiogram had been performed within the previous 5 years. Three-dimensional quantitative coronary angiography, QFR, and lesion length analysis were conducted on lesions responsible for the MI (future culprit lesions, [FCL]) as well as on control lesions (non-culprit lesions, [NCL]).

Results:



Eighty-three FCL and 117 NCL were analyzed in 83 patients: FCL were more severe (median % diameter of stenosis [DS] 39.1% [29.8; 45.7] vs. 29.8% [25.0; 37.2], p < .001), had lower QFR values (0.94 [0.86; 0.98] vs. 0.98 [0.96;

Figure 16

1.00], p < .001) and tended to be longer (15.2 mm [10.0; 27.3] vs. 12.7 mm [9.3; 22.4], p = .070) than NCL.

In lesions with an interval < 2 years between baseline angiography and MI, the difference in QFR was more pronounced compared to the lesions with a longer interval (FCL: 0.92 [0.85; 0.97] vs. NCL: 0.98 [0.94; 1.00], p < .001 and FCL: 0.96 [0.88; 1.00] vs. NCL: 0.98 [0.96;1.00], p = .006 respectively)

CONCLUSION: Mild coronary stenoses that are subsequently responsible for an MI (FCL) exhibit a higher DS and lower QFR years before the event. Furthermore, FCL with a lower QFR at baseline appear to lead earlier to MI.

6. CHAPTER IV : Beyond catheters use : FFR derived from CT

Introduction and overview of Chapter 4

In the previous chapter (Chapter 3), we saw data supporting the accuracy of angiography-derived FFR. One of the major advantages of these technologies is to avoid the risk associated with maneuvering a pressure wire down a coronary artery and the need to deliver hyperemic agents but still, these technologies require a coronary angiography, which remains an invasive procedure. In this context, the cardiac CT and the CT-derived FFR (FFR-CT) emerge as new promising tools.

In one of the landmark studies based on >200 patients with suspected stable CAD who underwent coronary CT and routine 3-vessel invasive FFR measurements, FFR-CT values were retrospectively derived from the coronary CT images (47). In this study, FFR-CT showed a diagnostic accuracy, sensitivity, and specificity of 87%, 90%, and 86% (per-vessel basis) and 78%, 96%, and 63% (per-patient basis). These results confirmed previous data based on >250 patients where per-patient sensitivity and specificity (95% CI) to identify myocardial ischemia were similar (86% (95% CI: 77% to 92%) and 79% (95% CI: 72% to 84%)) (48). This excellent accuracy was also confirmed in patients with 3-vessel CAD included in the SYNTAX II trial, even if FFR-CT was compared with iFR in this sub-study (49). The diagnostic accuracy of FFR-CT to detect functional significant stenosis based on an instantaneous wave-free ratio ≤0.89 revealed an area under the receiver-operating characteristics curve of 0.85 (95% CI: 0.79 to 0.90) with a sensitivity of 95% (95% CI: 89% to 98%) and a specificity of 61% (95% CI: 48% to 73%).

During this thesis, different works based on the role of cardiac CT for the evaluation of coronary artery stenoses have been conducted.

We started by a review (in French) on the contemporary role of CT in cardiology.

- Tzimas G, Meier D, Monney P, Roguelov C, Skalisis I, Muller O, **Fournier S**, Qanadli SD
  CT-scan in cardiology in 2019 : central role and other applications
  Rev Med Suisse. 2019 May 22;15(652):1060-1066

Then, as CT is routinely used to plan transcatheter aortic valve implantation (TAVI) procedures, we decided to investigate the performance of pre-TAVI CT for excluding coronary artery disease. Indeed, it is unclear whether CTA performed during the TAVI workup is accurate enough to exclude significant coronary artery disease allowing thus avoiding unnecessary invasive coronary angiography, which is particularly of interest among frailer and older patients with frequent comorbidities such as chronic renal failure. Accordingly, we retrospectively investigated the data of 127 patients in whom CT images were analyzed for the presence of ≥ 50% (significant CAD) and ≥ 70% (severe CAD) diameter stenoses in proximal coronary arteries. Results were compared with invasive coronary angiography at vessel and patient levels. The results of this study are presented hereafter and based on the abstract of the following consultation:

- Meier D, Depierre A, Topolsky A, Roguelov C, Dupré M, Rubimbura V, Eeckhout E, Qanadli SD, Muller O and **Fournier S**
  Computed tomography angiography for the diagnosis of coronary artery disease among patients undergoing transcatheter aortic valve implantation
  J Cardiovasc Transl Res . 2021 Feb 4. doi: 10.1007/s12265-021-10099-8.

In this study, 342 vessels were analyzed. The negative predictive value of the CT was 97.5% for significant CAD and 96.3% for severe CAD.

Finally, we designed a trial (and are still enrolling patients) in which we investigate the ability of FFR-CT to detect the absence of hemodynamically significant lesions in patients with high-risk acute coronary syndrome (ACS) admitted in the emergency department with chest pain. Indeed, the ACS without ST segment elevation (NSTE-ACS) patients represent a major diagnostic challenge as clinical assessment and ECG alone are not sufficient to confirm or exclude diagnosis in most patients. In this context, cardiac biomarkers such as troponin remain the cornerstone of an early diagnosis but the introduction of high-sensitive troponins (allowing to improve the diagnostic sensitivity of NSTE-AC) contributes to a high proportion of false positive (ie patients with a 'normal' invasive coronary angiography). We designed this trial to assess whether FFR-CT is able to identify among high-risk NSTE-ACS patients, those without hemodynamically significant coronary stenosis by invasive FFR. Indeed, it appeared that to date, FFR-CT has never been evaluated in high-risk NSTE-ACS patients.

In these patients, the benefit of an FFR-based strategy versus an angiography-based strategy to guide culprit stenosis treatment was investigated in a sub-analysis of the FAME study (50). Among the 1005 patients with multivessel disease included in the study, 328 had a NSTE-ACS. As compared to angiography-guided strategies, the 2-year risk reduction of major adverse cardiac events (MACE) with FFR-guided strategies was comparable between patients with unstable angina (UA)/NSTEMI and stable angina (absolute risk reduction of 5.1% versus 3.7%, respectively, P=0.92). Of interest, in patients with NSTE-ACS, an FFR-guided strategy reduced the number of stents and the use of contrast, without an increased procedural time. In addition, the FAMOUS-NSTEMI randomized trial ('Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction') included 350 NSTEMI patients with at least a 30% coronary stenosis assessed visually and randomized them into an FFR-guided group and into an angiography-guided group (51). In this study, the proportion of patients treated initially by medical therapy was higher in the FFR-guided group than in the angiography-guided group (22.7% versus 13.2%,

P=0.022). Noteworthy, FFR resulted in a change in the a priori (i.e. the planned treatment based on angiography alone) treatment in 21.6% of patients. At 12 months, revascularization remained lower in the FFR-guided group (79.0 versus 86.8%, P=0.054) but there were no statistically significant differences in health outcomes and quality of life between the 2 groups.

The design of this trial presented hereafter is based on following publication:

- Meier D, Skalidis I,De Bruyne B,Qanadli SD, Rotzinger D,Eeckhout E,Collet C,Muller O, **Fournier S.**

  Ability of FFR-CT to detect the absence of hemodynamically significant lesions in patients with high-risk NSTE-ACS admitted in the emergency department with chest pain, study design and rationale.

  Int J Cardiol Heart Vasc. 2020 Mar 5;27:100496.

Meier D, Depierre A, Topolsky A, Roguelov C, Dupré M, Rubimbura V, Eeckhout E, Qanadli SD, Muller O and **Fournier S**

Computed tomography angiography for the diagnosis of coronary artery disease among patients undergoing transcatheter aortic valve implantation

J Cardiovasc Transl Res . 2021 Feb 4. doi: 10.1007/s12265-021-10099-8.

Background: Computed tomography angiography (CTA) is used to plan TAVI procedures. We investigated the performance of pre-TAVI CTA for excluding coronary artery disease (CAD).

Methods: In total 127 patients were included. CTA images were analyzed for the presence of ≥ 50% (significant CAD) and ≥ 70% (severe CAD) diameter stenoses in proximal coronary arteries. Results were compared with invasive coronary angiography (ICA) at vessel and patient levels. Primary endpoint was the negative predictive value (NPV) of CTA for the presence of CAD.

Results: A total of 342 vessels were analyzable. NPV of CTA was 97.5% for significant CAD and 96.3% for severe CAD. Positive predictive value and accuracy were 44.8% and 87.1% for significant CAD and 56.3% and 94.4% for severe CAD. At patient level, NPV for significant CAD was 88.6%.

Conclusion: Pre-TAVI CTA shows good performance for ruling out CAD and could be used as a gatekeeper for ICA in selected patients.

Meier D, Skalidis I,De Bruyne B,Qanadli SD, Rotzinger D,Eeckhout E,Collet C,Muller O, **Fournier S.**

Ability of FFR-CT to detect the absence of hemodynamically significant lesions in patients with high-risk NSTE-ACS admitted in the emergency department with chest pain, study design and rationale.

Int J Cardiol Heart Vasc. 2020 Mar 5;27:100496.

Background: In the era of High-sensitive troponin (hs-Tn), up to 50% of patients with a mild increase of hs-Tn will finally have a normal invasive coronary angiogram. Fractional Flow Reserve (FFR) derived from coronary computed tomographic angiography (FFR-CT) has never been used as a non-invasive tool for the diagnosis of coronary artery disease in patients with high-risk acute coronary syndrome without ST segment elevation (NSTE-ACS).

Aims: The study aims to determine the role of coronary CT angiography and FFR-CT in the setting of high-risk NSTE-ACS.

Methodology: We will conduct a prospective trial, enrolling 250 patients admitted with high-risk NSTE-ACS who will rapidly undergo a coronary CT angiography and then a coronary angiography with FFR measurements. Results of coronary CT, FFR-CT and coronary angiography (± FFR) will be compared.

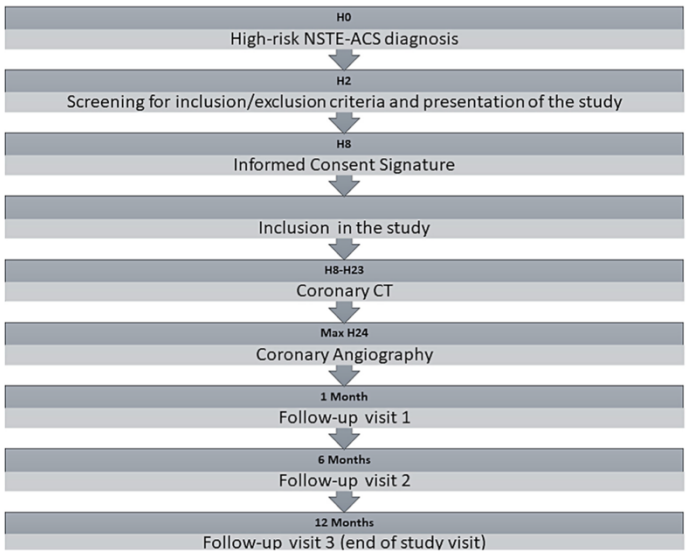


Figure 17

Potential significance: In conclusion, non-invasive identification of patients with high-risk NSTE-ACS who could avoid coronary angiography would reduce procedure related risks and medical costs.

Tzimas G, Meier D, Monney P, Roguelov C, Skalisis I, Muller O, **Fournier S**, Qanadli SD

CT-scan in cardiology in 2019 : central role and other applications

Rev Med Suisse. 2019 May 22;15(652):1060-1066

7. DISCUSSION

In the introduction, some of the limitations of FFR were listed, namely:

1) the lack of data supporting the benefit of FFR in terms of the reduction of hard endpoints and the lack of data supporting the benefits of FFR in the field of coronary artery bypass graft surgery

2) the absence of information obtained by FFR on the microcirculation

3) the risks associated with maneuvering a pressure wire down a coronary artery

4) the general risks associated with invasive coronary angiography

These 4 topics have been a large source of inspiration for this PhD thesis which started at the end of 2018. These limitations have also been the focus of interest of numerous research groups in recent years, yielding numerous publications that have changed our interpretation of these limitations 3 years later.

1) Regarding the lack of data supporting the benefit of FFR in terms of the reduction of hard clinical endpoints, the 5-year follow-up of the FAME 2 study and the pooled analysis of FAME 2, DANAMI-3-PRIMULTI and Compare-Acute (32-34) seem to support a benefit of FFR-guidance in terms of reduction in the number of future spontaneous myocardial infarctions: lesions with a low FFR have a higher probability of causing a myocardial infarction in the future. However, FFR is not the only predictor of future MI. In the EMERALD study, 72 patients with ACS and available coronary CT acquired between 1 month and 2 years before the ACS were analyzed. FFR derived from CT but also adverse plaque characteristics, wall shear stress and axial plaque stress were all significantly associated with future myocardial infarction (52). This finding was confirmed by a FAME 2 sub-study that we conducted in which we added wall shear stress on top of FFR among patients in the MT group (patients with significant lesions by FFR, treated with medical therapy only). We observed that in

patients with stable CAD and hemodynamically significant lesions, higher WSS had an incremental prognostic value over FFR (53). Accordingly, while it is probably true that FFR guidance allows a reduction in future MI, different parameters need to also be taken into account. Different groups are currently investigating if the processing of all these different parameters together with machine learning allows for better stratification.

In addition, the use FFR to guide the planning of CABG surgery is associated with a simplified procedure (demonstrated in randomized trials (8) and in retrospective studies (54)) with at least equivalent clinical outcomes (retrospective studies even indicate a potential benefit (38)).

2) Regarding the lack of data on microcirculation, the development of the RayFlow catheter used together with a regular FFR pressure wire allows – with continuous thermo-dilution – the measurement of both absolute flow and resistance, thus emerging as a real game changer in the evaluation of the microcirculation. During the last 3 years, its safety and its reproducibility have been demonstrated and “normal” values have also been published. Its contribution in the management of INOCA/ANOCA patients (Ischemia/Angina with Non-Obstructive Coronary Arteries) will probably rapidly be demonstrated. In the recently published EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation endorsed by the Coronary Vasomotor Disorders International Study Group, its use is already discussed in addition to regular metrics such as IMR (55). Furthermore, new concepts such as Microvascular Resistance Reserve (MRR) are currently being developed with the use of this new technology.

3) Angiography-derived FFR (e.g. FFR_{angio}, QFR,..) is a good alternative to FFR and its validity in specific settings where FFR has previously been tested is currently being investigated (severe aortic stenosis (56), non-culprit lesions in STEMI patients (57),…). Its adoption will probably increase the rate of “physiology”-guided PCI in situations where FFR cannot be measured.

4) FFR-CT has emerged as an excellent modality for the diagnosis of CAD. Its validity among NSTE-ACS patients is being investigated in a trial that we designed and for which we are still recruiting patients. Its adoption and its development will also probably contribute to an increase in the rate of “physiology”-guided PCI.

These new tools will probably help us to be less invasive overall when obtaining information on the hemodynamic impact of a stenosis (CT-derived FFR, angiography-derived FFR), all whilst justifying a more invasive approach when needed, such as in situations where a non-invasive assessment of the epicardial vessels is insufficient and when more information about the state of the microcirculation is needed.

In summary, these tools will permit a global and individualized evaluation of a patient’s coronary physiological.

8. REFERENCES

1. Zimmermann FM, Omerovic E, Fournier S, Kelbaek H, Johnson NP, Rothenbuhler M, et al. Fractional flow reserve-guided percutaneous coronary intervention vs. medical therapy for patients with stable coronary lesions: meta-analysis of individual patient data. Eur Heart J. 2019;40(2):180-6.
2. Fournier S, Juni P, De Bruyne B. PCI Guided by Fractional Flow Reserve at 5 Years. N Engl J Med. 2019;380(1):104-5.
3. Fournier S, Ciccarelli G, Toth GG, Milkas A, Xaplanteris P, Tonino PAL, et al. Association of Improvement in Fractional Flow Reserve With Outcomes, Including Symptomatic Relief, After Percutaneous Coronary Intervention. JAMA Cardiol. 2019;4(4):370-4.
4. Fournier S, Kobayashi Y, Fearon WF, Collet C, da Costa BR, Rioufol G, et al. Asymptomatic Patients With Abnormal Fractional Flow Reserve Treated With Medication Alone or With PCI. J Am Coll Cardiol. 2019;74(12):1642-4.
5. Milkas A, Rueda-Ochoa OL, Fournier S, Muller O, Van Rooij F, Franco OH, et al. 10-Year Survival After FFR-Guided Strategy in Isolated Proximal Left Anterior Descending Coronary Stenosis. J Am Coll Cardiol. 2019;74(10):1420-1.
6. Di Gioia G, De Bruyne B, Pellicano M, Bartunek J, Colaiori I, Fiordelisi A, et al. Fractional flow reserve in patients with reduced ejection fraction. Eur Heart J. 2020;41(17):1665-72.
7. Fournier S, Collet C, Xaplanteris P, Zimmermann FM, Toth GG, Tonino PAL, et al. Global Fractional Flow Reserve Value Predicts 5-Year Outcomes in Patients With Coronary Atherosclerosis But Without Ischemia. J Am Heart Assoc. 2020;9(24):e017729.
8. Toth GG, De Bruyne B, Kala P, Ribichini FL, Casselman F, Ramos R, et al. Graft patency after FFR-guided versus angiography-guided coronary artery bypass grafting: the GRAFFITI trial. EuroIntervention. 2019;15(11):e999-e1005.
9. Fournier S, Toth GG, Colaiori I, De Bruyne B, Barbato E. Long-Term Patency of Coronary Artery Bypass Grafts After Fractional Flow Reserve-Guided Implantation. Circ Cardiovasc Interv. 2019;12(5):e007712.
10. Fournier S, Toth GG, De Bruyne B, Kala P, Ribichini FL, Casselman F, et al. Changes in surgical revascularization strategy after fractional flow reserve. Catheter Cardiovasc Interv. 2021.
11. Fournier S, Colaiori I, Di Gioia G, Mizukami T, De Bruyne B. Hyperemic Pressure-Flow Relationship in a Human. J Am Coll Cardiol. 2019;73(10):1229-30.
12. Fournier S, Keulards DCJ, van 't Veer M, Colaiori I, Di Gioia G, Zimmermann FM, et al. Normal Values of Thermodilution-Derived Absolute Coronary Blood Flow and Microvascular Resistance in Humans. EuroIntervention. 2020.
13. Adjedj J, Picard F, Collet C, Bruneval P, Fournier S, Bize A, et al. Intracoronary Saline-Induced Hyperemia During Coronary Thermodilution Measurements of Absolute Coronary Blood Flow: An Animal Mechanistic Study. J Am Heart Assoc. 2020;9(15):e015793.
14. Keulards DCJ, Fournier S, van 't Veer M, Colaiori I, Zelis JM, El Farissi M, et al. Computed tomographic myocardial mass compared with invasive myocardial perfusion measurement. Heart. 2020;106(19):1489-94.
15. Candreva A, Gallinoro E, van 't Veer M, Sonck J, Collet C, Di Gioia G, et al. Basics of Coronary Thermodilution. JACC Cardiovasc Interv. 2021;14(6):595-605.

16. Candreva A, Gallinoro E, Fournier S, Izaga E, Finet G, De Bruyne B, et al. Absolute Blood Flow in the Left Main Coronary Artery and Its Distribution. JACC Cardiovasc Interv. 2021;14(4):482-4.
17. Gallinoro E, Candreva A, Colaiori I, Kodeboina M, Fournier S, Nelis O, et al. Thermodilution-Derived Volumetric Resting Coronary Blood Flow Measurement in Humans. EuroIntervention. 2021.
18. Fearon WF, Achenbach S, Engstrom T, Assali A, Shlofmitz R, Jeremias A, et al. Accuracy of Fractional Flow Reserve Derived From Coronary Angiography. Circulation. 2019;139(4):477-84.
19. Johnson NP, Matsumura M, Achenbach S, Engstrom T, Assali A, Jeremias A, et al. Angiography-Derived Fractional Flow Reserve Versus Invasive Nonhyperemic Pressure Ratios. J Am Coll Cardiol. 2019;73(24):3232-3.
20. Kobayashi Y, Collet C, Achenbach S, Engstrom T, Assali A, Shlofmitz RA, et al. Diagnostic Performance of Angiography-based Fractional Flow Reserve in Various Subgroups: Report from the FAST-FFR Study. EuroIntervention. 2020.
21. Rubimbura V, Guillon B, Fournier S, Amabile N, Chi Pan C, Combaret N, et al. Quantitative flow ratio virtual stenting and post stenting correlations to post stenting fractional flow reserve measurements from the DOCTORS (Does Optical Coherence Tomography Optimize Results of Stenting) study population. Catheter Cardiovasc Interv. 2020;96(6):1145-53.
22. Pagnoni M, Meier D, Candreva A, Maillard L, Adjedj J, Collet C, et al. Future culprit detection based on angiography-derived FFR. Catheter Cardiovasc Interv. 2021.
23. Tzimas G, Meier D, Monney P, Roguelov C, Skalidis I, Muller O, et al. [Cardiac CT in cardiology in 2019 : major role and extended applications]. Rev Med Suisse. 2019;15(652):1060-6.
24. Meier D, Depierre A, Topolsky A, Roguelov C, Dupre M, Rubimbura V, et al. Computed Tomography Angiography for the Diagnosis of Coronary Artery Disease Among Patients Undergoing Transcatheter Aortic Valve Implantation. J Cardiovasc Transl Res. 2021.
25. Meier D, Skalidis I, De Bruyne B, Qanadli SD, Rotzinger D, Eeckhout E, et al. Ability of FFR-CT to detect the absence of hemodynamically significant lesions in patients with high-risk NSTE-ACS admitted in the emergency department with chest pain, study design and rationale. Int J Cardiol Heart Vasc. 2020;27:100496.
26. Pijls NH, Van Gelder B, Van der Voort P, Peels K, Bracke FA, Bonnier HJ, et al. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. Circulation. 1995;92(11):3183-93.
27. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360(3):213-24.
28. Xaplanteris P, Fournier S, Pijls NHJ, Fearon WF, Barbato E, Tonino PAL, et al. Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. N Engl J Med. 2018;379(3):250-9.
29. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41(3):407-77.
30. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med. 2014;371(13):1208-17.
31. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and

management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2012;60(24):e44-e164.
32. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med. 2012;367(11):991-1001.
33. Smits PC, Abdel-Wahab M, Neumann FJ, Boxma-de Klerk BM, Lunde K, Schotborgh CE, et al. Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction. N Engl J Med. 2017;376(13):1234-44.
34. Engstrom T, Kelbaek H, Helqvist S, Hofsten DE, Klovgaard L, Holmvang L, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3-PRIMULTI): an open-label, randomised controlled trial. Lancet. 2015;386(9994):665-71.
35. Bogaty P. PCI Guided by Fractional Flow Reserve at 5 Years. N Engl J Med. 2019;380(1):102.
36. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40(2):87-165.
37. Barbato E, Toth GG, Johnson NP, Pijls NH, Fearon WF, Tonino PA, et al. A Prospective Natural History Study of Coronary Atherosclerosis Using Fractional Flow Reserve. J Am Coll Cardiol. 2016;68(21):2247-55.
38. Fournier S, Toth GG, De Bruyne B, Johnson NP, Ciccarelli G, Xaplanteris P, et al. Six-Year Follow-Up of Fractional Flow Reserve-Guided Versus Angiography-Guided Coronary Artery Bypass Graft Surgery. Circ Cardiovasc Interv. 2018;11(6):e006368.
39. Duncker DJ, Bache RJ. Regulation of coronary blood flow during exercise. Physiol Rev. 2008;88(3):1009-86.
40. Spaan JAE. Coronary blood flow : mechanics, distribution, and control: Springer-Science+Business Media, B.V.; 1991.
41. Fearon WF, Balsam LB, Farouque HM, Caffarelli AD, Robbins RC, Fitzgerald PJ, et al. Novel index for invasively assessing the coronary microcirculation. Circulation. 2003;107(25):3129-32.
42. Lee JM, Jung JH, Hwang D, Park J, Fan Y, Na SH, et al. Coronary Flow Reserve and Microcirculatory Resistance in Patients With Intermediate Coronary Stenosis. J Am Coll Cardiol. 2016;67(10):1158-69.
43. Aarnoudse W, Van't Veer M, Pijls NH, Ter Woorst J, Vercauteren S, Tonino P, et al. Direct volumetric blood flow measurement in coronary arteries by thermodilution. J Am Coll Cardiol. 2007;50(24):2294-304.
44. Barbato E, Dudek D, Baumbach A, Windecker S, Haude M. Current trends in coronary interventions: an overview from the EAPCI registries. EuroIntervention. 2017;13(Z):Z8-Z10.
45. Tu S, Westra J, Yang J, von Birgelen C, Ferrara A, Pellicano M, et al. Diagnostic Accuracy of Fast Computational Approaches to Derive Fractional Flow Reserve From Diagnostic Coronary Angiography: The International Multicenter FAVOR Pilot Study. JACC Cardiovasc Interv. 2016;9(19):2024-35.

46. Collet C, Onuma Y, Sonck J, Asano T, Vandeloo B, Kornowski R, et al. Diagnostic performance of angiography-derived fractional flow reserve: a systematic review and Bayesian meta-analysis. Eur Heart J. 2018;39(35):3314-21.
47. Driessen RS, Danad I, Stuijfzand WJ, Raijmakers PG, Schumacher SP, van Diemen PA, et al. Comparison of Coronary Computed Tomography Angiography, Fractional Flow Reserve, and Perfusion Imaging for Ischemia Diagnosis. J Am Coll Cardiol. 2019;73(2):161-73.
48. Norgaard BL, Leipsic J, Gaur S, Seneviratne S, Ko BS, Ito H, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol. 2014;63(12):1145-55.
49. Collet C, Miyazaki Y, Ryan N, Asano T, Tenekecioglu E, Sonck J, et al. Fractional Flow Reserve Derived From Computed Tomographic Angiography in Patients With Multivessel CAD. J Am Coll Cardiol. 2018;71(24):2756-69.
50. Sels JW, Tonino PA, Siebert U, Fearon WF, Van't Veer M, De Bruyne B, et al. Fractional flow reserve in unstable angina and non-ST-segment elevation myocardial infarction experience from the FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) study. JACC Cardiovasc Interv. 2011;4(11):1183-9.
51. Layland J, Oldroyd KG, Curzen N, Sood A, Balachandran K, Das R, et al. Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: the British Heart Foundation FAMOUS-NSTEMI randomized trial. Eur Heart J. 2015;36(2):100-11.
52. Lee JM, Choi G, Koo BK, Hwang D, Park J, Zhang J, et al. Identification of High-Risk Plaques Destined to Cause Acute Coronary Syndrome Using Coronary Computed Tomographic Angiography and Computational Fluid Dynamics. JACC Cardiovasc Imaging. 2019;12(6):1032-43.
53. Kumar A, Thompson EW, Lefieux A, Molony DS, Davis EL, Chand N, et al. High Coronary Shear Stress in Patients With Coronary Artery Disease Predicts Myocardial Infarction. J Am Coll Cardiol. 2018;72(16):1926-35.
54. Toth G, De Bruyne B, Casselman F, De Vroey F, Pyxaras S, Di Serafino L, et al. Fractional flow reserve-guided versus angiography-guided coronary artery bypass graft surgery. Circulation. 2013;128(13):1405-11.
55. Kunadian V, Chieffo A, Camici PG, Berry C, Escaned J, Maas A, et al. An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. Eur Heart J. 2020;41(37):3504-20.
56. Mejia-Renteria H, Nombela-Franco L, Paradis JM, Lunardi M, Lee JM, Amat-Santos IJ, et al. Angiography-based quantitative flow ratio versus fractional flow reserve in patients with coronary artery disease and severe aortic stenosis. EuroIntervention. 2020;16(4):e285-e92.
57. Lauri FM, Macaya F, Mejia-Renteria H, Goto S, Yeoh J, Nakayama M, et al. Angiography-derived functional assessment of non-culprit coronary stenoses in primary percutaneous coronary intervention. EuroIntervention. 2020;15(18):e1594-e601.

9. Figure legends

Figure 1 : Primary composite endpoint of cardiac death or myocardial infarction. The cumulative incidence of the primary endpoint of cardiac death or myocardial infarction was significantly reduced in subjects randomized to fractional flow reserve-guided percutaneous coronary intervention com- pared with medical therapy alone. Dashed lines are crude time-to-event curves and solid lines are fitted cumulative incidence curves as predicted from a mixed effects flexible parametric model. Only the fitted curves should be used for inferences about the treatment effect.

Figure 2 : A, Probability of improvement of at least 2 Canadian Cardiovascular Society classes at 1 month based on the change in fractional flow reserve. B, Correlation between the change in fractional flow reserve and vessel-oriented clinical events at 2 years.

Figure 3 : Time-to-events curves are shown for death or myocardial infarction (MI) in the different patient groups according to the presence or absence of angina at the time of randomization and to their treatment assignment.

Figure 4 : The inset shows a typical example of a stenosis in the proximal left anterior descending coronary artery. If the fractional flow reserve (FFR) had been >0.80, the patient would have been treated medically; if the FFR had been #0.80, the patient would have been revascularized. Solid lines indicate the revascularization group, and dashed lines indicate controls.

Figure 5 : Cumulative incidences and landmark analysis for MACCE and all-cause death. cumulative incidence of MACCE (A) and all- cause death (C); landmark analysis before and after 1 year timepoint for MACCE (B) and all-cause death (D). The dotted green line represents the control cohort with preserved LVEF, for visual comparison. P-values are referred to the fractional flow reserve-guided and the Angiography-guided groups.

Figure 6 : Kaplan-Meier graph reporting the cumulative incidence of major adverse cardiovascular events (MACEs) up to 5 years in the low global fractional flow reserve (FFR) group (green), mid global FFR group (red), and high global FFR group (blue). B, Kaplan-Meier graph reporting the cumulative incidence of revascularization up to 5 years in the low global FFR group (green), mid global FFR group (red), and high global FFR group (blue). C, Kaplan-Meier graph reporting the cumulative incidence of MACEs up to 5 years in patients with 0, 1, or 2 ≥50% stenoses at discharge (blue, red, and green, respectively). D, Kaplan-Meier graph reporting the cumulative incidence of revascularization up to 5 years in patients with 0, 1, or 2 ≥50% stenoses at discharge (blue, red, and green, respectively).

Figure 7 : Incidence of major adverse cardiovascular and cerebrovascular events during one-year clinical follow-up.

Figure 8 : The patency rate in all grafts (A, P value = 0.024) and in arterial grafts (B, P value = 0.028).

Figure 9 : (A) Plots of the corresponding hyperemic coronary driving pressure and flow values. Aortic pressure (Pa) (red) and distal coronary pressure (Pd) (green) are corrected for a measured coronary wedge pressure (Pw) of 20 mm Hg. Hyperemic flow (Qs) is shown in blue. (B) From the initial 11,000 values, only 200 are displayed after random sampling (see text for details). LAD 1⁄4 left anterior descending coronary artery.

Figure 10 : Hyperemic effect of saline infusion rates of 5, 10, 15, and 20 mL/min through the RayFlow catheter expressed in mean difference of percentage of change in absolute blood flow above the baseline as compared with hyperemia achieve with adenosine in the study vessel and in the control vessel.

Figure 11 : Within 10 s after the start of the infusion of saline at room temperature (arrows), a decline in distal temperature is observed. (Bottom right) Plot of the individual data and their agreement with the Passing-Bablok regression.

Figure 12 : Intraclass correlation (ICC) between mass and coronary blood flow with 95% CI bands.

Figure 13 : A, Correlation scatter plot with linear regres- sion, r=0.80. B, Bland–Altman plot with 95% confidence limits between −0.14 and 0.12 for the absolute differences. FFR indicates fractional flow reserve.

Figure 14 : A subject enrolled in the study whose dominant right coronary artery contains mild diffuse disease. Resting physiology remains normal with all nonhyperemic pressure ratios $0.92 despite an invasive fractional !ow reserve (FFR) of 0.70, matched by angiography-derived FFR (FFRangio) of 0.71.

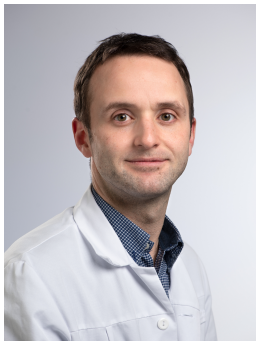
Figure 15 : Correlation between post- PCI QFR and post-PCI FFR.

Figure 16 : Relation between QFR and proportion of culprit vessels when dividing the cohort into quintiles of QFR. FCL, future culprit lesion; QFR, quantitative flow ratio

Figure 17 : Study Flow Chart

10. Curiculum Vitae with list of publications

Curriculum Vitae



1. Personal information

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Date of birth:	11 April 1987
Nationality:	Swiss
Marital status:	Married (Anne)
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Private number:	+41 79 703 67 62
Professional number :	+41 79 556 82 05
Private e-mail:	fournier.stephane@gmail.com
Professional e-mail :	stephane.fournier@chuv.ch

2. Titles

2020 : Privat Docent, University of Lausanne

2019 : Swiss Board of Cardiology Certification (FMH)

2013 : Doctor of Medicine, MD (thesis in cardiology, Dr Muller, University of Lausanne, Switzerland)

2012 : Swiss Federal Medical Diploma (University of Lausanne)

3. Education

2019-2021 : PhD candidate in the International CardioPath Programme

2017 : Post Doctoral Fellowship in Aalst, Belgium (with a grant from the Swiss National Science Foundation)

2012 : United States Medical Licensing Examination (USMLE) Step 2 (Clinical Knowledge)

2012 : Level 1 Swissmedic training as a clinical researcher

2007-2012 : Medical School, University of Lausanne, Switzerland. Master's degree in medicine, "STEMI : socio-economic factors and the race against time"

4. Positions

2018- : Resident physician, Interventional Cardiology, CHUV, Lausanne, Switzerland

2017- 2018 : Fellowship in clinical research & interventional Cardiology, Aalst, Belgium

2014-2016 : Resident physician, Cardiology Department, CHUV, Lausanne, Switzerland

2012–2014 : Resident physician, Internal Medicine Department at the CHUV, including: internal medicine, emergency, diabetology and angiology units

2011 : Medical trainee (Six months) in CHUV's Cardiology Department

2011 : Internship year as a trainee physician

5. Prizes and awards

2019 : Swiss Interventional Cardiology Award 2019

2018 : Young Investigator Award Coronary Pathophysiology and Microcirculation finalist at the ESC congress

2018 : Winner of the Moderated Posters Award at session « Complex Decisions in Coronary Intervention"

2018 : Oto Hess Trainee Award

2018 : Best abstract at the Belgian Society of Cardiology yearly meeting

2015 : Winner of the Moderated Posters Award at session « Reperfusion in STEMI » at the ESC congress

2014 : Marc Dufour Prize, awarded by the University of Lausanne for the MD thesis

2012 : Master's degree work awarded at the Lausanne Faculty of Biology and Medicine's Master Day

6. Grants

2019 : "Pépinière grant" (University of Lausanne and Lausanne University Center Hospital)

2019 : Porphyrogenis grant (University of Lausanne and private foundation)

2019 : Grant from the Vaudoise Foundation of Interventional Cardiology

2019 : Working Group on interventional cardiology, Swiss Society of Cardiogy

2016 : Swiss National Science Foundation : "Early Postdoc.Mobilty" (Grant P2LAP3_168469)

7. Board and committee membership

2020- : EAPCI Training & Certification Committee member

2020- : EAPCI Scientific Documents & Initiatives Committee member

2018 - : Swiss Ambassador at the EAPCI Young community (elected by the Swiss Working Group for Interventional Cardiology)

8. Academics

2020-2021 : Ex cathedra lessons : Medical treatment of coronary artery disease / Hemodynamic, from theory to practice (UNIL)

2019-2021 : Tutor of 2 Master's degree work (Medical School, UNIL)

2013-2018 : Co-tutor of 6 Master's degree work (Medical School, UNIL)

2011–2012 : Chairman of final year medical students group

2010–2012 : Tutor in Faculty of Biology and Medicine course on "Skills" for 2nd /3rd year medical students

2009–2011 : Student representative to the Faculty Council

2008–2010 : Tutor in Faculty of Biology and Medicine anatomy course for 1st /2nd year medical students

2008–2010 : Tutor in Faculty of Biology and Medicine radiology course for 2nd year medical students

2008–2009 : Vice-chairman of the Consultative Commission of Medical Students

2008–2009 : Vice-chairman of the University of Lausanne Medical Students Association

9. Editorial activities

1. : Circulation (reviewer)

2. : JACC (reviewer)

3. : JACC : Cardiovascular Interventions (reviewer)

4. : Circulation: Quality & Outcomes (reviewer)

5. : Heart (reviewer)

6. : JAHA (reviewer)
7. : American Journal of Cardiology (reviewer)
8. : EuroIntervention (reviewer)
9. : Journal of interventional cardiology (reviewer)
10. : BMJ open (reviewer)
11. : Chronobiology International (reviewer)
12. : Frontiers in Cardiovascular Medicine

10. Publications :

1. Articles

1. Candreva A, Pagnoni M, Rizzini ML, Mizukami T, Gallinoro E, Mazzi V, Gallo D, Meier D, Shinke T, Aben JP, Nagumo S, Sonck J, Munhoz D, **Fournier S**, Barbato E, Heggermont W, Cook S, Chiastra C, Morbiducci U, De Bruyne B, Muller O, Collet C.
   Risk of myocardial infarction based on endothelial shear stress analysis using coronary angiography.
   Atherosclerosis. 2021 Nov 16:S0021-9150(21)01437-4.

2. De Bruyne B, Pijls NHJ, Gallinoro E, Candreva A, **Fournier S**, Keulards DCJ, Sonck J, Van't Veer M, Barbato E, Bartunek J, Vanderheyden M, Wyffels E, De Vos A, El Farissi M, Tonino PAL, Muller O, Collet C, Fearon WF.
   Microvascular Resistance Reserve for Assessment of Coronary Microvascular Function: JACC Technology Corner.
   J Am Coll Cardiol. 2021 Oct 12;78(15):1541-1549.

3. Mahendiran T , Klingenberg R, Nanchen D, Gencer B, Meier D, Räber L, Carballo D, Matter C, Lüscher T, Mach F, Rodondi N, von Eckardstein A, Muller O, **Fournier S**
   CCN family member 1 (CCN1) is an early marker of infarct size and left ventricular dysfunction in STEMI patients
   Atherosclerosis. 2021 Oct;335:77-83.

4. **Fournier S,** Keulards DCJ, van 't Veer M, Colaiori I, Di Gioia G, Zimmermann FM, Mizukami T, Nagumo S, Kodeboina M, El Farissi M, Zelis JM, Sonck J, Collet C, Pijls NHJ, De Bruyne B.
   Normal Values of Thermodilution-Derived Absolute Coronary Blood Flow and Microvascular Resistance in Humans.
   EuroIntervention. 2021 Jul 20;17(4):e309-e316.

5. Kobayashi Y, Collet C, Achenbach S, Engstrøm T, Assali A, Shlofmitz RA, **Fournier S**, Kirtane AJ, Ali ZA, Kornowski R, Leon MB, De Bruyne B, Fearon WF
   Diagnostic performance of angiography-based fractional flow reserve by patient and lesion characteristics
   EuroIntervention. 2021 Jul 20;17(4):e294-e300.

6. Meier D, Mahendiran T, **Fournier S**
   Applicability of ISCHEMIA in real-world practice: Where to START?
   EuroIntervention. 2021 Jun 11;17(2):e181-e182

7. Toth GG, Johnson NP, Wijns W, Toth B, Achim A, **Fournier S**, Barbato E.
   Revascularization decisions in patients with chronic coronary syndromes: Results of the second international survey on interventional strategy (ISIS-2).
   Int J Cardiol. 2021 Aug 1;336:38-44

8. Kamani C, Firsova M, Akiba R, **Fournier S,** Duchini M, Prior JO.
Inflammation or Ischemia?: That Is the Question.
Circ Cardiovasc Imaging. 2021 May;14(5):e012164.

9. Lu H, Monney P, Hullin R, **Fournier S**, Roguelov C, Eeckhout E, Rubimbura V, Faroux L, Barrier A, Muller O, Kirsch M.
Transcarotid Access Versus Transfemoral Access for Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis.
Front Cardiovasc Med. 2021 May 27;8:687168

10. Pagnoni M, Meier D, Candreva A, Maillard L, Adjedj J, Collet C, Mahendiran T, Cook S, Mujcinovic A, Dupré M, Rubimbura V, Roguelov C, Eeckhout E, De Bruyne B, Muller O, **Fournier S**.
Future culprit detection based on angiography-derived FFR.
Catheter Cardiovasc Interv. 2021 Apr 29. Online ahead of print.

11. **Fournier S,** Toth GG, De Bruyne B, Kala P, Ribichini FL, Casselman F, Ramos R, Piroth Z, Piccoli A, Penicka M, Mates M, Nemec P, Van Praet F, Stockman B, Degriek I, Pellicano M, Barbato E.
Changes in surgical revascularization strategy after fractional flow reserve.
Catheter Cardiovasc Interv. 2021 Apr 10. Online ahead of print.

12. Lu H, **Fournier S**, Muller O, Roguelov C, Rosner L, Kapitanov A, Kirsch M.
The transcervical access for transcatheter aortic valve replacement.
J Card Surg. 2021 Jul;36(7):2533-2535.

13. Candreva A, Gallinoro E, van 't Veer M, Sonck J, Collet C, Di Gioia G, Kodeboina M, Mizukami T, Nagumo S, Keulards D, **Fournier S**, Pijls NHJ, De Bruyne B.
Basics of Coronary Thermodilution.
JACC Cardiovasc Interv. 2021 Mar 22;14(6):595-605.

14. Candreva A, Gallinoro E, **Fournier S,** Izaga E, Finet G, De Bruyne B, Gutiérrez-Barrios A.
Absolute Blood Flow in the Left Main Coronary Artery and Its Distribution.
JACC Cardiovasc Interv. 2021 Feb 22;14(4):482-484.

15. Meier D, Depierre A, Topolsky A, Roguelov C, Dupré M, Rubimbura V, Eeckhout E, Qanadli SD, Muller O and **Fournier S**
Computed tomography angiography for the diagnosis of coronary artery disease among patients undergoing transcatheter aortic valve implantation
J Cardiovasc Transl Res. 2021 Feb 4. Online ahead of print.

16. Gallinoro E, Candreva A, Colaiori I, Kodeboina M, **Fournier S**, Nelis O, Di Gioia G, Sonck J, van 't Veer M, Pijls NHJ, Collet C, De Bruyne B.
Thermodilution-Derived Volumetric Resting Coronary Blood Flow Measurement in Humans
EuroIntervention. 2021 Feb 2. Online ahead of print.

17. Kilani N, Haddad C, Lu H, Ghanbari F, Domenichini G, Pavon AG, Tzimas G, **Fournier S**, Hullin R, Pascale P, Eeckhout E, Schwitter J, Pruvot E, Bouchardy J, Monney P, Muller O, Rutz T.
Cardiology
Rev Med Suisse. 2021 Jan 27;17(723):172-180.

18. **Fournier S,** Collet C, Xaplanteris P, Zimmermann FM, Toth GG, Tonino PAL, Pijls NHJ, Colaiori I, Di Gioia G, Barbato E, Jüni P, Fearon WF, De Bruyne B.
Global FFR Value Predicts 5-Year Outcomes in Patients with Coronary Atherosclerosis but Without Ischemia
J Am Heart Assoc. 2020 Dec 15;9(24):e017729.

19. Lu H, **Fournier S**, Namasivayam J, Roguelov C, Ferrari E, Eeckhout E, Monney P, Tozzi P, Marcucci C, Muller O, Kirsch M.
Transapical approach versus transcervical approach for transcatheter aortic valve replacement: a retrospective monocentric study.
Interact Cardiovasc Thorac Surg. 2020 Dec 7;31(6):781-788.

20. Meier D, Mahendiran T, **Fournier S**
Will ISCHEMIA change our daily practice ?
Cardiovasc Diagn Ther. 2020 Aug;10(4):908-911

21. Bruggmann C, **Fournier S**, Panchaud A, Muller O, Sadeghipour F, Voirol P.
Beta-blocker use and up-titration after acute ST-segment elevation myocardial infarction: a cohort study.
Swiss Med Wkly. 2020 Aug 18;150:w20321

22. Adjedj J, Picard F, Collet C, Bruneval P, **Fournier S**, Bize A, Sambin L, Berdeaux A, Varenne O, De Bruyne B, Ghaleh B.
Intracoronary Saline-Induced Hyperemia During Coronary Thermodilution Measurements of Absolute Coronary Blood Flow: An Animal Mechanistic Study.
J Am Heart Assoc. 2020 Aug 4;9(15):e015793.

23. Pavon AG, Meier D, Samim D, Rotzinger DC, **Fournier S**, Marquis P, Monney P, Muller O, Schwitter
First Documentation of Persistent SARS-Cov-2 Infection Presenting With Late Acute Severe Myocarditis.
J.Can J Cardiol. 2020 Jun 6:S0828-282X(20)30532-8.

24. Pagnoni M, Meier D, **Fournier S**, Muller O.
[Chronic coronary syndrome (stable coronary artery disease) : Indication to revascularization in 2020 and latest evidence].
Rev Med Suisse. 2020 Jun 3;16(696):1140-1146.

25. Keulards DCJ*, **Fournier S***, van 't Veer M, Colaiori I, Zelis JM, El Farissi M, Zimmermann FM, Collet C, De Bruyne B, Pijls NHJ
Computed tomographic myocardial mass compared with invasive myocardial perfusion measurement.
Heart. 2020 Oct;106(19):1489-1494.
* equally contributed

26. Meier D, Domenichini G, Mahendiran T, Pagnoni M, Monney P, Pruvot E, Muller O, **Fournier S.**
Pandémie de COVID-19 : aspects cardiologiques
Rev Med Suisse. 2020 May 6;16(692):930-932.

27. Meier D*, **Fournier S***, Masci PG, Eeckhout E, Antiochos P, Tzimas G, Stoyanov N, Muenkaew M, Monney P, Schwitter J, Muller O, Harbaoui B.
Impact of manual thrombectomy on microvascular obstruction in STEMI patients.
Catheter Cardiovasc Interv . 2021 May 1;97(6):1141-1148
* equally contributed

28. Mahendiran T, Nanchen D, Meier D, Gencer B, Klingenberg R, Räber L, Carballo D, Matter CM, Lüscher TF, Windecker S, Mach F, Rodondi N, Muller O, **Fournier S.**
Optimal Timing of Invasive Coronary Angiography following NSTEMI.
J Interv Cardiol. 2020 Mar 3;2020:8513257.

29. Meier D, Skalidis I,De Bruyne B,Qanadli SD, Rotzinger D,Eeckhout E,Collet C,Muller O, **Fournier S.**
Ability of FFR-CT to detect the absence of hemodynamically significant lesions in patients with high-risk NSTE-ACS admitted in the emergency department with chest pain, study design and rationale.
Int J Cardiol Heart Vasc. 2020 Mar 5;27:100496.

30. Ravach G, **Fournier S**, Mazzolai L, Nanchen D.
Aspirin for primary cardiovascular prevention : the end of an era ?
Rev Med Suisse. 2020 Mar 4;16(684):459-462.

31. Johnson DT, **Fournier S,** Kirkeeide RL, De Bruyne B, Gould KL, Johnson NP.
Phasic pressure measurements for coronary and valvular interventions using fluid-filled catheters: Errors, automated correction, and clinical implications.
Catheter Cardiovasc Interv . 2020 Sep 1;96(3):E268-E277.

32. Meier D, **Fournier S**, Barras N, Regamey J, Rosset S, Pavon AG, Kamani CH, Deliniere A, Domenichini G, Graf D, Hullin R, Pascale P, Girod G, Eeckhout É, Schwitter J, Prior JO, Pruvot É, Bouchardy J, Monney P, Muller O, Rutz T.
Cardiology
Rev Med Suisse. 2020 Jan 15;16(676-7):16-22

33. Toth GG, De Bruyne B, Kala P, Ribichini FL, Casselman F, Ramos R, Piroth Z, **Fournier S,** Piccoli A, Van Mieghem C, Penicka M, Mates M, Nemec P, Van Praet F, Stockman B, Degriek I, Barbato E.
Graft patency after FFR-guided versus angiography-guided coronary artery bypass grafting. The GRAFFITI trial.
EuroIntervention. 2019 Dec 6;15(11):e999-e1005

34. Mahendiran T, Nanchen D, Gencer B, Meier D, Klingenberg R, Räber L, Carballo D, Matter CM, Lüscher T, Windecker S, Mach F, Rodondi N, Muller O, **Fournier S**
Prognosis of Patients With Chronic and Hospital-Acquired Anaemia After Acute Coronary Syndromes
J Cardiovasc Transl Res . 2020 Aug;13(4):618-628.

35. Rubimbura V, Guillon B, **Fournier S**, Amabile N, Chi Pan C, Combaret N, Eeckhout E, Kibler M, Silvain J, Wijns W, Schiele F, Muller O, Meneveau N, Adjedj J.
Quantitative flow ratio virtual stenting and post stenting correlations to post stenting fractional flow reserve measurements from the DOCTORS (Does Optical Coherence Tomography Optimize Results of Stenting) study population.
Catheter Cardiovasc Interv . 2020 Nov;96(6):1145-1153.

36. Interatrial septum dissection and atrial wall hematoma following transseptal puncture: A systematic review of the literature
Meier D, Antiochos P, Herrera-Siklody C, Eeckhout E, Delabays A, Tzimas G, **Fournier S**, Pascale P, Muller O, Monney P.
Catheter Cardiovasc Interv . 2020 Aug;96(2):424-431.

37. Tzimas G, Antiochos P, Monney P, Eeckhout E, Meier D, **Fournier S,** Harbaoui B, Muller O, Schläpfer J
Atypical Electrocardiographic Presentations in Need of Primary Percutaneous Coronary Intervention
Am J Cardiol. 2019 Oct 15;124(8):1305-1314

38. Muller O*, **Fournier S***, Pilgrim T, Heg D, Noble S, Jeger R, Toggweiler S, Taramasso M, Windecker S, Stortecky S (
Local versus general anesthesia for transcatheter aortic valve replacement : a SwissTAVI registry analysis
JACC Cardiovasc Interv. 2019 Sep 23;12(18):1874-1876.
(equally contributed)

39. **Fournier S** , Kobayashi Y, Fearon WF, Collet C, Roza da Costa B, Rioufol G, Pijls NHJ, Jüni P,De Bruyne B
Asymptomatic Patients with Abnormal Fractional Flow Reserve Treated with Medication Alone or with PCI
J Am Coll Cardiol. 2019 Sep 24;74(12):1642-1644.

40. Milkas A, Rueda-Ochoa OL, **Fournier S**, Muller O, Van Rooij, Franco OH, Collet C, Barbato E, Kavousi M, De Bruyne B
Ten-Year Survival After FFR-Guided Strategy in Isolated Proximal Left Anterior Descending Coronary Stenosis. Matched Comparison with Normal Individuals
J Am Coll Cardiol. 2019 Sep 10;74(10):1420-1421

41. Di Gioia G; De Bruyne B, Pellicano M, Bartunek J, Colaiori , Fiordelisi A, Canciello G, Xaplanteris P, **Fournier S**, Katbeh A, Franco D; Kodeboina M, Morisco C, Van Praet F, Casselman F, Degrieck I, Stockman B, Vanderheyden M; Barbato E
Fractional Flow Reserve in patients with reduced ejection fraction
Eur Heart J . 2020 May 1;41(17):1665-1672.

42. Johnson NP, Mahaera A, Achenbach S, Engstrom T, Assali A, Jeremias A, **Fournier S**, De Bruyne B, Leon MB, Fearon WF
Angiography-derived fractional flow reserve versus invasive non-hyperemic pressure ratios
J Am Coll Cardiol. 2019 Jun 25;73(24):3232-3233.

43. Tzimas G, Meier D, Monney P, Roguelov C, Skalisis I, Muller O, **Fournier S**, Qanadli SD
CT-scan in cardiology in 2019 : central role and other applications
Rev Med Suisse. 2019 May 22;15(652):1060-1066

44. **Fournier S,** Toth GG, Colaiori I, De Bruyne B, Barbato E
Long-term patency of coronary artery bypass graftsafter Fractional Flow Reserve guided implantation
Circ Cardiovasc Interv. 2019 May;12(5):e007712

45. Tzimas G, Eeckhout E, Antiochos P, Roguelov C, **Fournier S**, Harbaoui B, Monney P, Muller O.
Percutaneous Valvular Closure Followed by TAV-in-TAV Intervention during a Single Procedure in order to Treat a Severe Paravalvular Leak after Performing TAVI in a Bicuspid Aortic Stenosis.
Case Rep Cardiol. 2019 Apr 15;2019:4825607.

46. **Fournier S,** Colaiori I, Di Gioia g, Mizukami T, De Bruyne B
Hyperemic Pressure-Flow Relationship in Man
J Am Coll Cardiol. 2019 Mar 19;73(10):1229-1230.

47. Fournier S., Ciccarelli G., Toth GG, Milkas A., Xaplanteris P., Fearon WF., Pijls NHJ., Barbato E., De Bruyne B.
Association of Improvement in Fractional Flow Reserve With Outcomes, Including Symptomatic Relief, After Percutaneous Coronary Intervention.
JAMA Cardiol. 2019 Apr 1;4(4):370-374

48. Fearon WF, Achenbach S , Engstrom T , Assali A, Shlofmitz R , Jeremias A , **Fournier S** , Kirtane AJ, Kornowski R , Greenberg G , Jubeh R , Kolansky DM , McAndrew T , Dressler O, Maehara A , Matsumura M , Leon MB , De Bruyne B
Accuracy of Fractional Flow Reserve Derived From Coronary Angiography
Circulation. 2019 Jan 22;139(4):477-484.

49. Antiochos P, Barras N, Regamey J, Bisch L, Le Bloa M, Hullin R, Monney P, Schwitter J, Pascale P, Pruvot É, Eeckhout É, Muller O, **Fournier S.**
The year in cardiology : 2018
Rev Med Suisse. 2019 Jan 9;15(N° 632-633):27-30

50. Zimmermann FM, Omerovic E, **Fournier S**, Kelbæk H , Johnson NP, Xaplanteris, P, Abdel-Wahab M, Barbato E, Høfsten DE, Boxma-de Klerk BM, Fearon WF, Køber L, Pieter C, Smits PC, De Bruyne B, Pijls NHJ MD, Engstrøm T
Fractional Flow Reserve-Guided Percutaneous Coronary Intervention Versus Medical Therapy to Reduce Cardiac Death and Myocardial Infarction.
Eur Heart J. 2019 Jan 7;40(2):180-186

51. **Fournier S,** Jüni P, De Bruyne B
PCI Guided by Fractional Flow Reserve at 5 Years.
N Engl J Med. 2019 Jan 3;380(1):104-105.

52. Nishi T, Piroth Z, De Bruyne B, Jagic N, Möbius-Winkler S, Kobayashi Y, Derimay F, **Fournier S**, Barbato E, Tonino P, Juni P, Pijls NHJ, Fearon WF
Fractional Flow Reserve and Quality-of-Life Improvement after Percutaneous Coronary Intervention in Patients With Stable Coronary Artery Disease
Circulation. 2018 Oct 23;138(17):1797-1804.

53. Kumar A, Thompson EW, Lefieux A, Molony DS, Davis EL, Chand N, **Fournier S**, Lee HS, Suh J, Sato K, Ko YA, Molloy D, Chandran K, Hosseini H, Gupta S, Milkas A, Gogas B, Chang HJ, Min JK, Fearon WF, Veneziani A, Giddens DP, King SB 3rd, De Bruyne B, Samady H.
High Coronary Shear Stress in Patients With Coronary Artery Disease Predicts Myocardial Infarction
J Am Coll Cardiol. 2018 Oct 16;72(16):1926-1935

54. Harbaoui B, Nanchen D, Lantelme P, Gencer B, Heg D, Klingenberg R, Räber L, Carballo D, Matter CM, Windecker S, Mach F, Rodondi N, Eeckhout E, Monney P, Antiochos P, Schwitter J, Pascale P, **Fournier S**, Courand PY, Lüscher TF, Muller O.
Prognostic value of pulse pressure after an acute coronary syndrome.
Atherosclerosis. 2018 Oct;277:219-226.

55. Toth GG; De Bruyne B; Kala P; Ribichini F; Casselman F; Ramos R; Piroth Z; **Fournier S**; Van Mieghem C; Penicka M; Mates M; Van Praet F; Degriek I; Barbato E. Study design of the GRAft patency after FFR-guided versus angiography-guIded CABG TrIal.
J Cardiovasc Transl Res. 2018 Aug;11(4):269-273

56. Xaplanteris P*, **Fournier** S*, Pijls NHJ, Fearon WF, Barbato E, Tonino PAL, Engstrøm T, Kääb S, Dambrink JH, Rioufol G, Toth GG, Piroth Z, Witt N, Fröbert O, Kala P, Linke A, Jagic N, Mates M, Mavromatis K, Samady H, Irimpen A, Oldroyd K, Campo G, Rothenbühler M, Jüni P, De Bruyne B; FAME 2 Investigators. (* **equally contributed**)
Five-Year Outcomes with PCI Guided by Fractional Flow Reserve.
N Engl J Med. 2018 Jul 19;379(3):250-259.

57. **Fournier S**, Guenat F, Fournier A, Alberto L, Bonny O, Calderara Bertaggia D, Bardy D, Lauriers N, Harbaoui B, Monney P, Pascale P, Eeckhout E, Muller O
Circadian variation of ticagrelor-induced platelet inhibition in healthy adults
Eur Heart J Cardiovasc Pharmacother. 2018 Jul 1;4(3):166-171.

58. **Fournier S**, Toth GG, De Bruyne B, Johnson NP, Ciccarelli G, Xaplanteris P, Milkas A, Strisciuglio T, Bartunek J, Vanderheyden M, Wyffels E, Casselman F, Van Praet F, Stockman B, Degrieck I, Barbato E.
Six-Year Follow-Up of Fractional Flow Reserve-Guided Versus Angiography-Guided Coronary Artery Bypass Graft Surgery.
Circ Cardiovasc Interv. 2018 Jun;11(6):e006368

59. **Fournier S**, Roguelov C, Monney P, Kirsch M, Eeckhout E, Antiochos P, Lamsidri S, Muller O.
TAVI in 2018 : new indications and open questions
Rev Med Suisse. 2018 May 23;14(608):1097-1100

60. Ciccarelli G, Barbato E, Toth G, Gahl B, Xaplanteris P, **Fournier S**, Milkas A, Bartunek J, Vanderheyden M, Pijls N, Tonino P, Fearon WJ, Jüni P, De Bruyne B
Angiography versus Hemodynamics to Predict the Natural History of Coronary Stenoses. A FAME 2-Substudy.
Circulation. 2018 Apr 3;137(14):1475-1485.

61. **Fournier S**, Muller O, Benedetto U, Roffi M, Pilgrim T, Eberli FR, Rickli H, Radovanovic D, Erne P, Cook S, Noble S, Fesselet R, Zuffi A, Degrauwe S, Masci P, Windecker S, Eeckhout E, Iglesias JF; on behalf on the AMIS Plus Investigators.
Circadian dependence of manual thrombus aspiration benefit in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention.
Clin Res Cardiol. 2018 Apr;107(4):338-346

62. Yerly P, Adjedj J, **Fournier S**, Hullin R, Kirsch M, Masci PG, Monney P, Müller O, Regamey J, Schwitter J, Vogt P.
Cardiology update 2017
Rev Med Suisse. 2018 Mar 28;14(600):705-711

63. Xaplanteris P, **Fournier S**, Keulards DCJ, Adjedj J, Ciccarelli G, Milkas A, Pellicano M, Van't Veer M, Barbato E, Pijls NHJ, De Bruyne B.
Catheter-Based Measurements of Absolute Coronary Blood Flow and Microvascular Resistance: Feasibility, Safety, and Reproducibility in Humans.
Circ Cardiovasc Interv. 2018 Mar;11(3):e006194.

64. Pfister R, Weitsch S, **Fournier S**
An unusual cause of dysphagia
Eur J Cardiothorac Surg. 2018 Mar 1;53(3):692

65. Pouillot C, **Fournier S**, Glasenapp J, Rambaud G, Bougrini K, Vi Fane R, Geyer C, Adjedj J.
Pressure Wire Versus Microcatheter for FFR Measurement: A Head-to-Head Comparison.
EuroIntervention. 2018 Feb 2;13(15):e1850-e1856

66. **Fournier S**, Iten L, Marques-Vidal P, Boulat O, Bardy D, Beggah A, Calderara R, Morawiec B, Lauriers N, Monney P, Iglesias JF, Pascale P, Harbaoui B, Eeckhout E, Muller O
Circadian rhythm of blood cardiac troponin T concentration.
Clin Res Cardiol. 2017 Dec;106(12):1026-1032

67. **Fournier S,** Monney P, Roguelov C, Ferrari E, Eeckhout E, Muller O, Durko A, Van Mieghem N, Kappetein A, Margey R
How should I treat an Edwards Sapien 3 aortic valve embolization during a transaortic transcatheter aortic valve implantation ?
EuroIntervention 2017;13:495-498

68. Morawieck B, **Fournier S**, Tapponnier M, Prior J.0. , Monney P. , Dunet V, Lauriers N , Recordon F, Trana C, Iglesias JF, Kawecki D, Boulat O, Bardy D, Lamsidri S, Eeckhout E, Hugli O, Muller O
Performance of high sensitive cardiac troponin T assay to detect ischemia at PET-CT in low-risk patients with acute coronary syndrome: a prospective diagnostic study.
BMJ Open. 2017 Jul 10;7(7):e014655.

69. De Bruyne B, **Fournier S**, Barbato E.
Real-Life Fractional Flow Reserve.
Circulation. 2017 Jun 6;135(23):2252-2254.

70. **Fournier S**, Iglesias Juan F, Garelli V, Guinat M, Trana C, Muller O, Masci PG, Pascale P, Hugelshofer S, Degrauwe S, Roguelov C, Eeckhout E, Zuffi A
Coronary spasm-induced recurrent ventricular fibrillation: insights into possible mechanisms by a multimodality approach
Coron Artery Dis. 2017 May;28(3):268-271

71. **Fournier S**, Harbaoui B, Muller O
Letter by Fournier et al Regarding Article, "Functional Assessment of Coronary Artery Disease in Patients Undergoing Transcatheter Aortic Valve Implantation: Influence of Pressure Overload on the Evaluation of Lesions Severity".
Circ Cardiovasc Interv. 2017 Apr;10(4)

72. **Fournier S**, Iglesias JF, Zuffi A, Eeckhout E, Tozzi P, Muller O
Entrapment of Rotational Atherectomy Burrs in Freshly Implanted Stents: First Illustration of the Rolled-Up Phenomenon
J Invasive Cardiol. 2016 Nov;28(11):E132-E133.

73. Haas C, **Fournier S**, Iglesias JF,Trana C, Roguelov C,Locca D,Lauriers N, Muller O, Eeckhout E.
Assessment of quality performance measures for primary percutaneous coronary intervention: A report from a tertiary referral centre in Switzerland
Eur Heart J Acute Cardiovasc Care. 2016 Oct;5(6):435-442

74. Zuffi A, Muller O, Biondi-Zoccai G, Turri M, Trana C, Iglesias JF, **Fournier S**
Recanalization of a challenging chronic total occlusion of the superficial femoral artery through the profunda femoris using a pure retrograde approach
J Vasc Interv Radiol. 2016 Aug;27(8):1253-7

75. Antiochos P, Monney P, **Fournier S**, Roguelov C, Qanadli S, Eeckhout E, Muller O.
Endovascular management of heavily calcified abdominal aorta dissection during transcatheter aortic valve implantation.
Cardiol J. 2016;23(6):655-656.

76. **Fournier S**, Muller O.
Circadian aspects of myocardial infarction among young STEMI patients
Eur J Intern Med. 2016 Jan;27:e5-6

77. **Fournier S**, Regamey J, Rotman S, Pruvot E, Hullin R.
Cardiac Sarcoidosis with Celiac Disease
Cardiovascular Medicine. 2016;19(04):128-131

78. **Fournier S**, Muller O
The impact of fractional flow reserve and iFr on current PCI strategies
Cardiovascular Medicine. 2016;19(03):67-71.

79. Zuffi A, Iglesias JF, Muller O, Agostoni P, Zoccai GB, Eeckhout E, **Fournier S.**
Interosseous artery collaterals and their support to ulno-palmar arch: A case report and a review of the literature
Int J Cardiol. 2015 Oct 15;197:280-1

80. **Fournier S,** Monney P, Roguelov C,Zuffi A, Iglesias JF, Qanadli SD,Courbon C,Eeckhout E,Muller O
First Reported Successful Femoral Valve-in-Valve Transcatheter Aortic Valve Replacement Using the Edwards Sapien 3 Valve
J Invasive Cardiol. 2015 Oct;27(10):E220-3

81. **Fournier S**, Muller O.
Commentary "Recent advances in circadian rhythms in cardiovascular system"
Front Pharmacol. 2015 Jun 26;6:132

82. **Fournier S**, Monney P, Ferrari E, Iglesias JF, Roguelov C, Zuffi A, Eeckhout E, Muller O
Transcatheter aortic valve implantation (TAVI): update on the indications
Rev Med Suisse. 2015 May 27;11(476):1197-1202

83. **Fournier S**, Taffé P, Radovanovic D, Von Elm E, Morawiec B, Stauffer JC, Erne P, Beggah A, Monney P, Pascale P, Iglesias JF, Eeckhout E, Muller O.
Myocardial infarct size and mortality depend on the time of day-a large multicenter study
PLoS One. 2015 Mar 11;10(3):e0119157

84. Kawecki D, Morawiec B, Monney P, Pellaton C, Wojciechowska C, Jojko J, Basiak M, Przywara-Chowaniec B, **Fournier S**, Nowalany-Kozielska E, Schwitter J, Muller O.
Diagnostic contribution of cardiac magnetic resonance in patients with acute coronary syndrome and culprit-free angiograms.
Med Sci Monit. 2015 Jan 14;21:171-80

85. **Fournier S**., Beggah A., Cook S., Muller O
Influence of circadian rhythms on myocardial infarctions
Rev Med Suisse. 2014 May 28;10(432):1204, 1206-9

86. **Fournier S.** , Puricel S. , Morawiec B. , Eeckhout E. , Mangiacapra F. , Trana C. , Tapponnier M. , Iglesias JF. , Michiels V , Stauffer J-C. , Beggah A. , Monney P. , Gobet S., Vogt P. , Cook S., Muller O.
Relationship between time of day and periprocedural myocardial infarction after elective angioplasty
Chronobiol Int. 2014 Mar;31(2):206-13

87. Duchini M, **Fournier S**, Iglesias JF, Roguelov C, Muller O, Eeckhout E.
Recurrent very late drug-eluting stent thrombosis
Int J Cardiol. 2013 Oct 9;168(4):e111-2

88. **Fournier S**, Taffé P, Muller O.
Ischemic Burden in ST Elevation Myocardial Infarction and Circadian Rhythms
Circ Res. 2013 Aug 2;113(4):e42

89. **Fournier S**., Muller O., De Palma R., Lauriers N., Eeckhout E.
Influence of socioeconomic factors on delays, management and outcome amongst patients with acute myocardial infarction undergoing primary percutaneous coronary intervention
Swiss Med Wkly. 2013;143:w13817

90. **Fournier S**., Muller O.
FAME II : intégrer la FFR à notre pratique quotidienne
(FAME II: integrating FFR in daily practice) Cardio Consensus for practitioners
Consensus Cardio pour le praticien - N° 87 , Mars 2013

91. **Fournier S.,** Muller O.
Finding the real culprit between circadian rhythm and "out of hours effect" to explain the higher myocardial infarction's size amongst patients with symptom onset occurring by night
Circulation Research 2012 Apr 27;110(9):e67

92. **Fournier S**., Eeckhout E., Mangiacapra F., Trana C., Lauriers N., Beggah AT., Monney P., Cook S., Bardy D., Vogt P., Muller O.
Circadian variations of ischemic burden among patients with myocardial infarction undergoing primary percutaneous coronary intervention
Am Heart J. 2012 Feb;163(2):208-13

93. **Fournier S**., Gaillard T., Joliat GR., Pittier R., Sarraj R.
L'attente aux urgences : causes, conséquences et solutions.
Waiting times in the emergency unit: causes, consequences and solutions
PrimaryCare.2010;10(2):33

2. Chapters in Books

1. TURBO Médecine d'urgences 2019
   Chapter : Cardiology

2. SURFméd Guidelines Médecine Interne 2019
   Chapter : Cardiology

3. Muller O, **Fournier S**, De Bruyne B
   Oxford Textbook of Interventional Cardiology (2nd edition)
   Editors : Martyn Thomas, Nick Curzen and Simon Redwood.
   Chapter 16, Coronary Physiology in Clinical Practice. 2016 (in press)

3. Oral presentations at conferences

1. **GRCI 2021 (Paris)**
   Fournier A
   FFR-CT in diabetic patients

2. **GHT 2021 (Online)**
   Fournier S
   State of the art lecture : Current concepts on the pathophysiology of coronary artery disease

3. **TCT 2019 (San Francisco)**
   Fournier S
   FFR-guided PCI in asymptomatic patients

4. **Congress of the Swiss Society of Cardiology 2019 (Interlaken)**
   Fournier S.
   FFR : overused or underused ?

5. **APPAC 2019 (Biarritz)**
   Fournier S.
   Minimal Immediate Mechanical Interventions (MIMI)

6. **ESC 2018 (Munich)**
   Fournier S., Kobayashi Y., Fearon WF., Roza da Costa B., Collet C., Xaplanteris P., Zimmerman F., Barbato E , Rioufol G, Pijls NHJ., Jüni P. & De Bruyne B.
   PCI reduces death/myocardial infarction in stable patients with silent ischemia

7. **ESC 2018 (Munich)**
   Fournier S., Collet C., Xaplanteris P., Zimmermann F., Toth GG., Tonino PAL., Pijls NHJ, Colaiori I., Di Gioia G., Barbato E., Fearon WF., Jüni P. and De Bruyne B.
   Global FFR Predicts Outcomes in Patients with Stable Coronary Artery Disease and no Ischemia

8. **ESC 2018 (Munich)**
   Fournier S., Toth G., De Bruyne B., Ciccarelli G., Xaplanteris .P, Milkas A., Strisciuglio T., Bartunek J., Vanderheyden M., Wyffels E., Casselman F., Van Praet., Stockman . Degriek I., Barbato E.
   Six-year follow-up of Fractional Flow Reserve-guided versus angiography-guided Coronary Artery Bypass Graft surgery

9. **APPAC 2018 (Biarritz)**
   Fournier S.
   RayFlow Catheter

10. EuroPCR 2018 (Paris)
Fournier S., Toth G., De Bruyne B., Ciccarelli G., Xaplanteris .P, Milkas A., Strisciuglio T., Bartunek J., Vanderheyden M., Wyffels E., Casselman F., Van Praet., Stockman . Degriek I., Barbato E.
Six-year follow-up of Fractional Flow Reserve-guided versus angiography-guided Coronary Artery Bypass Graft surgery

11. EuroPCR 2018 (Paris)
Fournier S., Ciccarelli G., Milkas A., Xaplanteris P., Fearon WF., Pijls NHJ., Barbato E., De Bruyne B.
Improvement in FFR predicts 2 years outcome after PCI. A FAME 2 Sub-Analysis.

12. Belgian Society of Cardiology 2018 (Brussels)
Fournier S., Ciccarelli G., Milkas A., Xaplanteris P., Fearon WF., Pijls NHJ., Barbato E., De Bruyne B.
Improvement in FFR predicts 2 years outcome after PCI. A FAME 2 Sub-Analysis.

13. Belgian Society of Cardiology 2018 (Brussels)
Fournier S., Toth G., De Bruyne B., Ciccarelli G., Xaplanteris .P, Milkas A., Strisciuglio T., Bartunek J., Vanderheyden M., Wyffels E., Casselman F., Van Praet., Stockman . Degriek I., Barbato E.
Six-year follow-up of Fractional Flow Reserve-guided versus angiography-guided Coronary Artery Bypass Graft surgery

14. AimRadial 2017 (Stuttgart)
Fournier S.
FFRangio

15. ESC Congress 2017 (Barcelone)
Fournier S., Ciccarelli G., Milkas A., Xaplanteris P., Fearon WF.,Pijls NHJ., Barbato E.,De Bruyne B.
Improvement in FFR predicts 2 years outcome after PCI. A FAME 2 Sub-Analysis.

16. London Valves 2016 (London)
Fournier S., Ferrari E., Roguelov C., Eeckhout E., Muller O.
A transaortic approach complication case during TAVI: its management and differences with other routes

17. ESC Congress 2016 (Rome)
Fournier S., Delabays A., Girod G., Muller O., Lo Ka Y., Roguelov C., Eeckhout E.
An unusual complication after percutaneous closure of a mitral para-annular / valvular leak

18. ESC Congress 2016 (Rome)
Fournier S., Ferrari E., Roguelov C., Eeckhout E., Muller O.
A transaortic approach complication case during TAVI: its management and differences with other routes

19. EuroPCR 2016 (Paris)
Fournier S., Benedetto U., Zuffi A., Radovanovic D., Erne P., Eeckhout E., Muller O., Iglesias J.F.
Circadian impact of manual thrombus aspiration on myocardial infarction size in patients with STEMI undergoing primary PCI : a propensity-matched score analysis of the Acute Myocardial Infarction in Switzerland registry

20. EuroPCR 2016 (Paris)
Fournier S., Ferrari E., Roguelov C., Eeckhout E., Muller O.
A transaortic approach complication case during TAVI: its management and differences with other routes

21. EuroPCR 2016 (Paris)
Fournier S., Delabays A., Girod G., Muller O., Lo Ka Y., Roguelov C., Eeckhout E.
An unusual complication after percutaneous closure of a mitral para-annular / valvular leak

22. ESC Congress 2015 (London)
Fournier S., Iglesias J-F. ; Degrauwe S., Eeckhout E., Muller O.
Entrapment of a rotablation burr in a freshly implanted stent extracted surgicall

23. ESC Congress 2015 (London)
Fournier S., Hugelshofer S., Degrauwe S., Marques-Vidal P., Radovanovic D., P. Erne P., Eeckhout E., Muller O., Iglesias J F.
Circadian variation of intracoronary thrombus aspiration efficacy in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention

24. Congress of the Swiss Society of Cardiology 2015 (Zurich)
Fournier S., Iten L., Marques-Vidal P., Boulat O., Beggah A., Calderara R., Morawiec., Eeckhout E., Monney P., Iglesias J-F., Pascale P., Lauriers N., Muller O.
CIRculating CArdiac TROponin T exhibits a circadian rhythm in healthy Population : the CircaTrop study

25. EuroPCR 2015 (Paris)
Fournier S., Iglesias J-F. ; Degrauwe S., Eeckhout E., Muller O.
Entrapment of a rotablation burr in a freshly implanted stent extracted surgically

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If everything seems under control,

you're just not going fast enough.