UNIVERSIDADE D COIMBRA FACULDADE DE MEDICINA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

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Pressure-wire based functional assessment of coronary stenoses in surgical heart valve disease patients: impact in the coronary revascularization technique

ARTIGO CIENTÍFICO ORIGINAL

ÁREA CIENTÍFICA DE CARDIOLOGIA

Trabalho realizado sob a orientação de:

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ABRIL/2019

PRESSURE-WIRE BASED FUNCTIONAL ASSESSMENT OF CORONARY STENOSES IN SURGICAL HEART VALVE DISEASE PATIENTS: IMPACT IN THE CORONARY REVASCULARIZATION TECHNIQUE

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List of Abbreviation

AS - Aortic Stenosis

BMI - Body Mass Index

CABG - Coronary Artery Bypass Grafting

CAD - Coronary Artery Disease

EACTS - European Association for Cardio-Thoracic Surgery

ESC - European Society of Cardiology

FFR - Fractional Flow Reserve

ICA - Invasive Coronary Angiography

iFR - Instantaneous Wave-free Ratio

LAD - Left Anterior Descending artery

PCI - Percutaneous Coronary Intervention

VHD - Valvular Heart Disease

Abstract

Aims: Describe how the pressure-wire based functional assessment of intermediate coronary stenoses affected the strategy of myocardial revascularization and to perform a one-year analysis in terms of cardiovascular events: cardiovascular death, myocardial infarction and unplanned revascularization.

Methods: We conducted a retrospective analysis on a prospective cohort of 32 patients with valvular heart disease out of 298 patients who underwent a pressure-wire based functional assessment of coronary stenosis between October 2013 and February 2018. The baseline data were extracted from two main databases. The median follow-up was 421 days. The cut-off values of 0.80 and 0.89 were used for FFR and iFR, respectively.

Results: We included 32 patients with valvular heart disease, which of 42 coronary lesions were functionally assessed by FFR and/or IFR. There were 23 male and 9 female patients and the median age was 73 (66.0-78.0) years. Regarding risk factors for cardiovascular diseases, 81.3% of the patients had hypertension, 81.3% were dyslipidemic, 18.8% were smokers and 31.3% were diabetic. The most frequent lesion was on the left anterior descending coronary artery, affecting 23 (54.8%) patients. Only 9 lesions were classified as hemodynamically significant and 6 of them were treated, either by PCI or CABG. The 33 remaining lesions didn't have an indication for revascularization, however, one lesion was treated with CABG. There were no major cardiovascular events within 12 months of follow-up.

Conclusion: In our centre, the cardiothoracic surgeons believe and act accordingly to the functional assessment evaluation of the coronary lesions. During the follow-up time, no cardiovascular events were registered among the patients which coronary physiological measurements were negative, confirming the safe use of FFR or iFR in this population with valvular heart disease.

Keywords: Coronary artery disease, heart valve diseases, coronary artery bypass, percutaneous coronary intervention, coronary angiography, fractional flow reserve.

Resumo

Objetivos: Descrever de que forma a informação obtida pela realização de avaliação funcional por guia de pressão afetou a estratégia de revascularização cirúrgica das artérias estudadas e realizar o seguimento clínico, a um ano, em termos de eventos cardio e cerebrovasculares: morte cardiovascular, enfarte agudo do miocárdio e revascularização não planeada.

Métodos: Foi conduzida uma análise retrospetiva de um coorte prospetivo de 32 doentes com doença valvular cardíaca, de um grupo de 298 doentes submetidos a uma avaliação funcional de estenoses coronárias intermédias por guia de pressão no nosso centro entre outubro de 2013 e fevereiro de 2018. As características dos doentes foram retiradas de duas bases de dados. O tempo médio de seguimento clínico foi de 421 dias. Na análise dos dados usaram-se como valores de referência de FFR e IFR um *cut-off* de ≤0,80 e de ≤0,89, respetivamente.

Resultados: Neste estudo foram incluídos 32 doentes com doença valvular cardíaca com indicação cirúrgica, tendo sido avaliadas através do FFR e/ou iFR 42 lesões coronárias. Foram integrados 23 doentes do sexo masculino e a idade média foi de 73 anos. Relativamente aos fatores de risco para doença cardiovascular, 81,3% dos doentes tinham hipertensão, 81,3% eram dislipidémicos, 31,3% tinham diabetes *mellitus* e 18,8% eram fumadores. A descendente anterior foi a artéria coronária mais vezes envolvida, afetando 23 (54,8%) doentes. Apenas 9 lesões foram classificadas como sendo hemodinamicamente significativas e 6 dessas foram revascularizadas. As 33 lesões restantes não tinham indicação para serem tratadas, no entanto 1 lesão foi revascularizada cirurgicamente.

Conclusão: No nosso centro os cirurgiões cardíacos acreditam e atuam consoante os resultados da avaliação funcional. Após um ano de seguimento clínico não se registaram eventos cardiovasculares *major* nos doentes cuja avaliação funcional tinha sido negativa, confirmando a segurança da utilização do FFR e iFR nesta população com doença valvular grave.

Palavras-chave: Doença coronária, doença valvular cardíaca, cirurgia de revascularização miocárdica, intervenção coronária percutânea, angiografia coronária, reserva fraccionada de fluxo coronário.

Introduction

Around 40% of patients with valvular heart disease (VHD) have concomitant coronary artery disease (CAD).[1] The revascularization of hemodynamically significant coronary stenosis is an important therapeutic option in surgical VHD patients with CAD.[2] In accordance with ESC/EACTS guidelines of 2017 for the management of VHD, coronary artery bypass grafting (CABG) is recommended in patients with a primary indication for aortic or mitral valve surgery and concomitant coronary artery diameter stenosis over 70% (Class-IC-recommendation).[3]

It has been reported that the combination of CABG with cardiac valve surgery carries an increased risk of mortality over isolated valve surgery.[1,4,5] The higher risk of the combined valvular and coronary surgery was associated with the effects of pre-existing ischemic myocardial damage and comorbidities.[1] This also means that the patients' comorbidity profiles affect survival more than the procedure itself. Of note, due to the increasing life expectancy, currently the patients with VHD are older and are more likely to have multivalvular disease and more comorbidities.

Invasive coronary angiography (ICA) is recommended in all patients with VHD requiring valve surgery[1] and is also the gold standard for the diagnosis of coronary stenosis, but it has a few limitations. This visual evaluation of the coronary lesions is very subjective and is associated with large inter-observer variability.[2] Conversely, a physiology-guided revascularization strategy has become a standard practice in the management of patients with CAD for more than 20 years ago when the fractional flow reserve (FFR) had been introduced.[6,7]

FFR is an invasive method using a pressure wire and a vasodilator agent which provides a direct functional assessment of coronary stenosis. This method permits the identification of myocardial ischemia, measurable at the time of clinical decision making. Recently, another physiological index, the instantaneous wave-free ratio (iFR), which does not require a hyperemic agent, was introduced.[7,8] Recent studies showed non-inferiority of iFR when compared with FFR. It was also established a significant correlation between iFR and the gold standard FFR, with a good performance of iFR identifying FFR-positive stenosis. Along with FFR, iFR was recently added as a Class-IA-recommendation in the ECS/EACTS guidelines of 2018 on myocardial revascularization.[2,7]

After evaluation by FFR or iFR, intermediate-grade coronary artery stenosis should not be revascularized if negative for ischemia.[9] Therefore, surgical coronary revascularization in patients undergoing valvular surgery should only be sought if there are functionally significant stenoses, as the combined coronary and valvular surgery carries an increased mortality risk.[1]

Notwithstanding that fact, the available evidence on FFR and IFR role as invasive physiologic indexes to assess CAD in patients with VHD is limited to a few small-scale observational studies. These studies support the feasibility of FFR and iFR in these patients.[10,11] However, the available evidence is insufficient to support the use of invasive functional assessment of coronary stenosis in patients with VHD, especially in patients with aortic stenosis (AS) since they have an altered haemodynamic.[9] Therefore, the role of such techniques in these patients is yet to be determined.[12]

The purpose of this study is to investigate the impact of the FFR and IFR evaluation on the revascularization technique used by surgeons in surgical VHD patients.

Methods

Study protocol

We conducted a single-institution retrospective observational analysis on a prospective cohort. Between October 2013 and February 2018, a total of 298 patients underwent a pressure-wire based functional assessment of coronary stenosis. Of these, 32 VHD patients were assessed, yielding a total of 42 coronary lesions. Patients gave consent to the use of anonymized data for research purpose at the time of the ICA.

Patients' data, including their clinical profile and ICA reports, were extracted from October 18th, 2017 to February 15th, 2019 from a main database of the Cardiology department and from the national population registries. The study population was thereafter followed up over a median of 421 days.

Demographics

For all patients we analyzed the following variables: age, gender, ventricular ejection fraction, body mass index (BMI), creatinine level, hypertension, diabetes, dyslipidemia, smoker, previous ischemic heart disease, previous revascularization, multivessel disease, non-ST segment elevation myocardial infarction, coronary physiological indexes, affected coronary segment, measured vessel location, revascularization technique performed.

Angiographic and functional assessment

The lesions evaluated functionally had angiographic evidence of significant CAD (≥ 50% stenosis). Afterwards, all coronary physiologic measurements were performed. An FFR ≤0.80 or an iFR ≤0.89 were considered "positive", pointing a hemodynamically significant lesion that mandated revascularization.

Endpoints

The co-primary endpoints were: (1) if the surgeons followed the suggestion of the functional-based assessment of the coronary stenosis for a conservative (or invasive) management; (2) a combined endpoint of one-year death from any cause, myocardial infarction or unplanned revascularization.

Statistical analysis

The continuous variables had a non-normal distribution so they were presented as median with interquartile range (IQR) boundaries. We described categorical variables as absolute frequencies and percentages. The follow-up period was calculated from the date of the ICA to the date of the last contact, for each patient. All the analyses were performed with SPSS version 23.0 (IBM inc., New York, USA).

Results

There were 32 patients with VHD in this study; 23 (71.9%) were males and 9 were females. Median age was 73 (66.0-78.0) years. Median BMI was 25.9 (23.7-29.9) $kg.m^{-2}$. Table 1 shows the baseline characteristics of patients. Regarding risk factors for cardiovascular diseases, 26 (81.3%) had hypertension, 26 (81.3%) were dyslipidemic, 6 (18.8%) were smokers and 10 (31.3%) were diabetic. Eight (25%) patients had previously underwent PCI or CABG and 14 (43.8%) patients had multivessel disease.

Table 1. Baseline characteristics of patients

Patients (N=32)	
General characteristics	
Age (years)	73 (66.0-78.0)
Male	23 (71.9)
Ejection fraction (%)	55 (49.5-59.3)
BMI ($kg.m^{-2}$)	25.9 (23.7-29.9)
Creatinine (mg/dL)	0.94 (0.80-1.21)
Cardiovascular risk factors	
Hypertension	26 (81.3)
Diabetes mellitus	10 (31.3)
Dyslipidemia	26 (81.3)
Smoker	6 (18.8)
Previous myocardial infarction	4 (12.5)
Previous PCI/CABG	8 (25.0)
Clinical presentation	
NSTEMI	1 (3.1)
Multivessel disease	14 (43.8)

Values are presented as n (%) or median (interquartile range).
BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; NSTEMI, non-ST segment elevation myocardial infarction.

The functional assessment with FFR and/or iFR was performed in 42 coronary lesions (23.8% guided by FFR, 71.4% guided by iFR and 4.8% guided by FFR/iFR). The most frequent lesion was on the left main coronary artery territory in 23 (54.8%) patients, namely the proximal and mid segments of the left anterior descending coronary artery (LAD).

Of the 42 lesions, only 9 (21.4%) were classified as hemodynamically significant, i.e. the FFR/iFR measurements were “positive”, thus amenable to revascularization (Table 2). Six (66.6%) of them were treated, either by PCI or CABG. Three patients were not accepted for cardiac surgery. Thirty-two lesions were not revascularized, following the functionally guided indication for conservative management. However, one lesion with negative FFR was treated with CABG (Fig.1).

Over 12 months of follow-up there were no cardiovascular events registered.

Table 2. Baseline characteristics of lesions and functional assessment

Lesions (N=42)	
Coronary physiologic parameters	
FFR	10 (23.8)
iFR	30 (71.4)
FFR and iFR	2 (4.8)
Measured vessel location	
Left anterior descending artery	23 (54.8)
Left circumflex artery	8 (19.0)
Right coronary artery	11 (26.2)
Hemodynamically significant lesions	9 (21.4)
Treatment of evaluated lesions	
Revascularization performed	7 (16.7)
PCI	5 (71.4)
CABG	2 (28.6)

Values are presented as n (%) or median (interquartile range).
FFR, fractional flow reserve; iFR, instantaneous wave-free ratio.

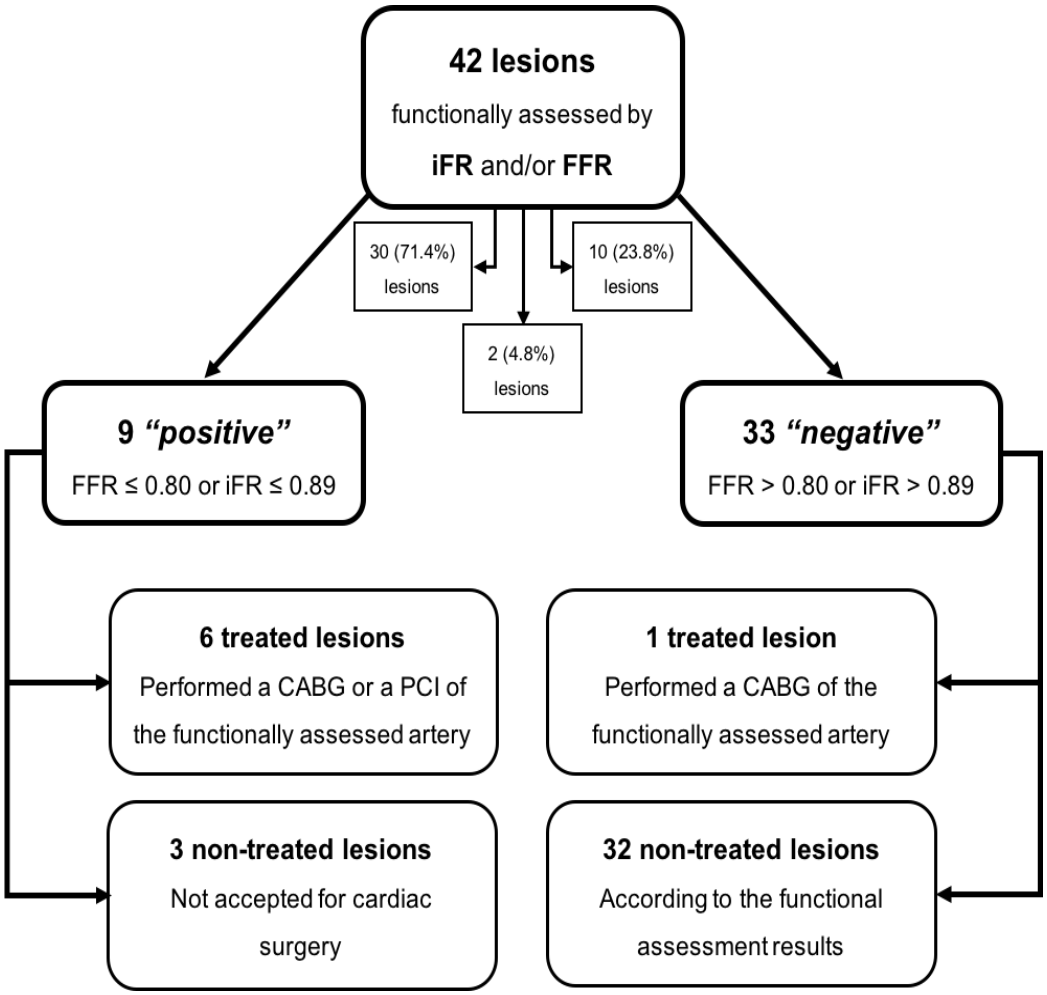

Figure 1 - Flow diagram representing the study results.

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio.

Discussion

According to our results, the cardiothoracic surgeons follow and act accordingly to the functional assessment of the coronary lesions. In fact, out of 42 FFR/iFR-assessed lesions, just one was treated contrary to the FFR/iFR indication. Taking in consideration the increased morbidity of a combine coronary and valve surgery, the sparing of unnecessary coronary revascularization procedures may well have a prognostic impact.

It is known that the combination of CABG with heart valve surgery carries an increased risk of mortality over isolated valve surgery.[1,4,5] Also, the revascularization by CABG requires a rigorous assessment of coronary artery disease.[13] Thus, an accurate assessment of intermediate-grade coronary stenosis is best achieved with pressure-wire based functional measurements such as FFR or iFR. However, FFR or iFR are not routinely performed prior to CABG[13] and, as far as we know, there are no published randomized controlled trials that have examined the use of these tools to guide CABG in this setting.

Nevertheless, some small observational studies support the applicability of FFR to patients planned to undergo CABG.[13,14,15] These studies further suggest that the incidence of functionally significant multivessel disease is decreased by FFR, resulting in fewer bypass grafts, reduced graft occlusion and less angina.[15] Likewise, according to FAME study,[16] performing PCI on all stenosis identified by angiography, even on the stenotic lesions that do not induce ischemia, diminishes the benefit of relieving ischemia by exposing the patient to an increased stent-related risk. Thus, systematic FFR measurement can maximize the benefit of PCI by accurately discriminating the lesions for which PCI may increase the risk from those for which revascularization will provide the most benefit. Furthermore, some other investigations demonstrated that FFR can successfully identify lesions that can safely be managed conservatively, among angiographically moderate stenoses[17]. This is confirmed by the reduction in unplanned revascularization and myocardial infarction with FFR-guided revascularization when compared with revascularization guided by angiography.

In our study, there were no major cardiovascular events within 12 months of follow-up, supporting the safe use of the pressure wire based functional assessment of coronary stenoses in patients with VHD. In a recent retrospective investigation by Di Gioia *et al.*[18], the management of selected patients with CAD and AS was significantly impacted by the FFR measurement, resulting in the deferral of aortic valve replacement being more patients treated with PCI. In patients who underwent CABG, FFR-guidance resulted in less venous grafts and anastomoses without increasing adverse event rates up to 5 years.

So far, there is only one ongoing randomized trial designed to assess the impact of FFR-guided revascularization in patients with valvular disease (SAVE-IT trial). The aim of this study is to determine, in patients undergoing elective valvular surgery, if the revascularization of the coronary artery disease guided by FFR would be superior to standard angiography-guided revascularization approach concerning to major efficacy and safety outcomes.[19]

Limitations

The present study has some design limitations, as it is a retrospective observational single-centre analysis. It was also conducted on a limited number of patients. Larger populations could provide greater statistical power.

Conclusion

Our findings suggest that (1) a pressure-wired based assessment of intermediate coronary stenoses in surgical VHD patients is safe and provides reliable information about the functional relevance of coronary lesions, with no coronary events at 12 months in patients with functionally negative lesions; (2) the surgeons supported a physiology-based revascularization strategy and that (3) 80% intermediate lesions in this cohort are functionally negative. If a strategy based on FFR/iFR deferral of coronary revascularization in the setting of surgical VHD disease is better regarding hear outcomes as the current angiographic-based system remains yet to be proven.

Agradecimentos

Agradeço à minha orientadora Professora Doutora Elisabete Jorge pela dedicação na orientação deste trabalho. Um sincero obrigada pela prontidão, energia e motivação que me deu ao longo deste percurso.

À Dra. Célia Domingues, minha co-orientadora, agradeço a disponibilidade e ajuda na realização deste projeto. O seu apoio foi fundamental para a concretização deste trabalho.

Agradeço à minha família, em especial aos meus pais, irmã e avó, por serem modelos de coragem e dedicação, pelo seu apoio incondicional e incentivo para perseguir os meus sonhos, por constantemente me lembrarem que *"pelo sonho é que vamos".*

Agradeço ao Daniel por ter caminhado ao meu lado, pela sua paciência, compreensão e ajuda fundamentais para a elaboração deste trabalho, por sempre me dar a mão.

E, por último, agradeço a todos os meus amigos, em especial à Sofia e à Carolina, que tanto me motivaram ao longo deste percurso. Um sincero obrigada por estarem sempre presentes nas etapas mais importantes da minha vida e por me incentivarem a ultrapassar todos os obstáculos.

Pelo sonho é que vamos,
comovidos e mudos.
Chegamos? Não chegamos?
Haja ou não haja frutos,
pelo sonho é que vamos.
Basta a fé no que temos.
Basta a esperança naquilo
que talvez não teremos.
Basta que a alma demos,
com a mesma alegria,
ao que desconhecemos
e ao que é do dia a dia.
Chegamos? Não chegamos?
– Partimos. Vamos. Somos.

Sebastião da Gama

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