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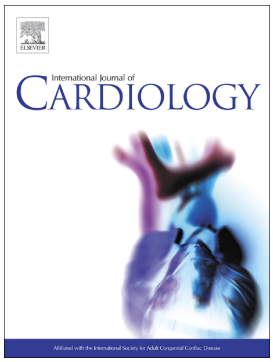

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Influence of Heart Rate on FFR Measurements: An Experimental and Clinical Validation Study

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Abstract

Background: Functional lesion assessment in stable coronary disease is considered the gold standard. The result of fractional flow reserve (FFR) in stable coronary disease is often a decision-maker for patient qualification. Taking into account the paramount position of FFR, it is crucial to acknowledge and reduce all potential bias.

Aims: In the present study, we quantified the influence of elevated HR on FFR results using a preclinical model and then validated the results in a clinical setting.

Methods and results: The relationship between FFR and HR was first explored experimentally in a porcine model. A clinical validation study was conducted in patients with isolated moderate lesions in the left anterior descending artery (LAD) or right coronary artery (RCA). In both the experimental and clinical arms, FFR was measured at resting HR and with pacing at 100, 130, 160, and 180 (for pigs) beats per minute. In the porcine model and in the clinical settings, a significant correlation between FFR and HR was confirmed in the LAD ($r=0.89$, $p<0.0001$; $r=0.53$, $p=0.00002$), but not in the RCA ($r=-0.19$, $p=0.5$; $r=0.14$, $p=0.3$). Post hoc analyses revealed that the FFR values in the LAD at 130/min and above tended to be significantly different from the baseline HR.

Conclusions: The results of this study indicate that in an experimental setting, tachycardia might be responsible for an overestimation of FFR results in LAD lesions.

Abbreviations

FFR: fractional flow reserve

HR: heart rate

iFR: instantaneous wave-free ratio

LAD: left anterior descending artery

OMT: optimal medical therapy

Pa: aortic (proximal) pressure, the pressure measured at the ostium of the left or the right coronary artery

Pd: distal pressure, the pressure measured distally to the lesion

PCI: percutaneous coronary intervention

RCA: right coronary artery

rFR: resting rull-cycle ratio

sCAD: stable coronary disease

Introduction

Over the past 40 years, physiological assessment of coronary lesions has developed with anatomic measures to guide revascularization decisions [1]. Coronary stenosis severity and coronary flow measures have been integrated into fluid dynamic equations and are thoroughly described in both experimental models and the clinical setting [2-5] Functional lesion assessment is the accepted gold standard in clinical decision-making regarding stable coronary disease (sCAD). Angiography alone provides only a partial picture as evidenced by the COURAGE study, which demonstrated a lack of additional benefit to percutaneous coronary interventions (PCI) over medical treatment in low-risk sCAD [6]. The FAME and FAME2 studies further demonstrated that lesions without impaired fractional flow reserve (FFR) do not confer poor prognosis or impaired quality of life [7-9].

FFR is a pressure-derived estimate of relative flow reserve [1]. Technically, it is a mean pressure ratio measured during maximal steady-state hyperemia. To achieve stable hyperemia,

pharmacological agents such adenosine or papaverine are introduced into the coronary circulation [10].

Coronary arterial blood flow occurs primarily during diastole and drops almost to zero or sometimes may be even reversed for a short period of time during systole [11, 12]. Elevated strain of the cardiac muscle and its shortening and thickening during contraction accompanied by high intraventricular pressure are responsible for systolic flow impairment. While the duration of systole remains nearly constant regardless of the heart rate (HR), the duration of diastole is highly dependent on the HR [13].

The instantaneous value of the distal to the aortic pressure ratio (Pd/Pa) approximates 1 at the moment of systole when the flow is close to zero. In steady-state fluid dynamics, zero flow implies no pressure gradient. As the HR increases, the ratio of systole to diastole increases, mostly as a consequence of the decrease in diastolic time. Thus, the FFR index, calculated as the mean Pd/Pa over the whole cardiac cycle, might by biased by an elevated HR. There is justified concern that the HR, as per its influence on a systolic-diastolic ratio, might affect FFR results. This is especially relevant considering the impact that even small changes in FFR can have on revascularization strategies that are recommended by current guidelines.

We aimed to experimentally evaluate the potential influence of the HR on FFR in both the right coronary artery (RCA) and left anterior descending artery (LAD) regions in both a porcine coronary model and a clinical setting.

Methods

Preclinical phase

This study was conducted at the Center for Cardiovascular Research and Development, American Heart of Poland. The study protocol was approved by the local Bioethics Committee.

We utilized a balloon-based in-stent stenosis animal model to explore the influence of the heart rate on the FFR measurement. After a diagnostic angiography, stent placement sites were selected taking into account the absence of curves or significant side branches. Next, Stentys stents (3.0-3.5 mm) were implanted in selected zones of the RCA and LAD. A regular wire was replaced with a pressure wire (St. Jude Medical) and a 2.5 mm or 3.0 mm balloon (in accordance with the vessel diameter) was introduced into the stented RCA and LAD segments. The balloon's position was verified by angiography. Intravenous adenosine infusion at a standard dose of 140 ug/kg/min was started to induce hyperemia. Normally it took 2-3 minutes to achieve stable hyperemia, after which the balloon was slowly inflated to achieve significant and stable stenosis as measured by FFR. The target FFR value was in the range of 0.7 to 0.8. In addition, a temporary pacing electrode was placed in the right ventricle to test FFR at different heart rates. FFR measurements were taken at the native HR and then again after pacing HRs, increasing by increments of 20 bpm up to 180 bpm. The balloon was kept in the artery for 5 minutes, after which at least three FFR measurements were taken for each HR. The same procedure was repeated in both the RCA and LAD.

In total, 33 FFR measurements were taken in 3 healthy domestic pigs weighing 72 SD 5.3 kg. A fourth animal was excluded from further evaluation because of ventricular fibrillation that occurred at the start of the procedure. All of the procedures were conducted under general anesthesia. The animals were previously intubated and mechanically ventilated. Cardiac catheterization was performed through standard femoral access, and 6F right Judkins catheters

were used. A pacing electrode was introduced into the right ventricle through a 7F sheath placed in the femoral vein.

Clinical phase

Nine elective patients with isolated and moderate lesions located in the LAD or RCA were included in the clinical arm of the study. The inclusion criteria included age younger than 75 years and the presence of a pacemaker or the patients' acceptance of temporary pacing. All of the patients enrolled met the inclusion criteria and signed an informed consent form. None of the included patients had severe valvular heart disease, ventricular hypertrophy, impaired systolic myocardial function, or anemia, which might have affected the FFR results.

Three patients had previously implanted cardiac pacemakers. In the remainder of cases, a temporary pacing electrode was introduced into the right ventricle via a femoral vein puncture. Adenosine was administered at a standard dose of 140 ug/min/kg in a peripheral vein. All of the FFR measurements were performed after stable hyperemia was reached. The FFR measurements were repeated three times for each heart rate, starting from the resting HR (mean: 59.2, SD 5.6) and during pacing at 100, 130, and 160 beats per minute.

Statistical analysis

Statistical analysis was done using Statistica 13.0 (Tibco). Linear regression analysis was performed for both the animal and clinical data. ANOVA with post hoc analyses was conducted in the clinical arm, the Bonferroni's correction was applied to address the multiple comparison issue. The clinical and demographic data were compared using Fisher's exact test for categorical outcomes and the Mann-Whitney U test for continuous outcomes. A p value of <0.05 was considered statistically significant. In the preclinical arm, assuming an effect size of $r=0.7$, it was determined that 30 measurements in each group would achieve 90% power.

Results

Porcine preclinical model

FFR was measured repeatedly at different heart rates (**Table 1**) utilizing a balloon-based in-stent stenosis model. The animal results (**Figure 1b**) indicated a relatively strong positive correlation between FFR and HR in the LAD ($r=0.89$, $p<0.00001$). In contrast, the results achieved in the RCA (**Figure 1a**) indicated no significant correlation between FFR and HR ($r=-0.19$, $p=0.5$).

Clinical verification

The baseline clinical features and demographic data of the enrolled patients are shown in **Table 2.** With the exception of age, there were no significant differences between the LAD and RCA groups. As per the protocol, the FFR measurements were recorded at a gradually increasing HR in the LAD and RCA lesions (**Table 1**). The results achieved in the LAD lesions (**Figure 1d**) indicated a moderate but statistically significant correlation between FFR and HR ($r=0.53$, $p=0.00002$). However, the results achieved in the RCA (**Figure 1c**) confirmed a lack of a significant correlation between FFR and HR as previously demonstrated in experimental settings ($r=0.14$, $p=0.3$). However, the observed FFR to HR relationship was numerically weaker than the relationship demonstrated in the animal model.

The FFR results achieved for each HR in the RCA and LAD were also pooled and variance analysis (ANOVA) was conducted (Figure 2a and 2b). Significant differences were shown in the LAD ($p=0.0002$) but not in RCA ($p=0.46$), as anticipated. Post hoc analyses revealed that FFR in the LAD starts to be significantly different from a baseline for HRs over 130/min.

Discussion

To the best of our knowledge, this is the first study to demonstrate a significant correlation between FFR and HR in the LAD. The results of the FAME and FAME 2 studies showed the importance of physiological coronary assessment to guide revascularization. Widely accepted consensus presented by the guidelines recommends against percutaneous or surgical revascularization in intermediate lesions if the lesion is not physiologically significant [14-16]. FFR has become the gold standard for the physiological assessment of coronary arteries [14, 16]. When FFR is above 0.8, optimal medical therapy (OMT) is preferred over percutaneous or surgical revascularization [14, 15]. Considering the weight of decision-making ascribed to FFR, it is essential to identify any potential factors that may influence this measurement.

If the influence of the HR on FFR is taken into account, clinicians may be especially sensitive to decision-making when FFR is borderline at a relatively high HR. Practically speaking, this finding may be especially relevant in the FFR gray zone (considered 0.75 to 0.80). For example, Shiono et al. [17] reported that patients with a gray zone FFR accompanied by deferral of revascularization are at higher risk of target vessel failure (mainly due to the revascularization rate) than those with FFR >0.80. It is possible that additional factors including heart rate could play a role in decision-making in cases with FFR between 0.75 and 0.80.

Although the significant influence of the HR on the flow reserve is a known physiological phenomenon [18, 19], the literature examining the role of the HR on FFR is sparse. Several small studies failed to identify a relationship between FFR and the HR [11, 20, 21]. Only one of these studies involved human subjects [11]. The group was relatively small (n=13) and

included a relatively limited range of HRs (80-110). Additionally, the results were not stratified by coronary artery, whereas in the present study, we found that the correlation between FFR and the HR was significant in the LAD but not the RCA. Blood flow in the LAD takes place mostly during diastole and drops to zero or is even reversed for a short time during systole [11, 12]. Elevated strain of the cardiac muscle, its shortening and thickening during contraction accompanied by high intraventricular pressure, is responsible for obstructing microcirculation during systole. However, systolic reduction of blood flow in the RCA is much less evident due to the right ventricle low-pressure territory that is supplied by the RCA [12, 22].

Among the previously published animal studies that failed to identify the relationship between the HR and FFR [11, 20, 21], the studied lesions were created by inflating a balloon in a coronary artery. A normal healthy artery is in a constant state of physiological adaptation to actual flow and myocardial oxygen demand. It is possible that because of this ongoing adaptation, a correctly sized balloon positioned in a healthy artery will not generate a functionally stable lesion. This may explain the observations of Peelukhana et al. that at the same HR and with the same balloon, the FFR measurements varied from 0.3 to nearly 1.0 [21]. The lack of a functionally stable lesion model may be the cause of the poor correlation between the HR and FFR in these preclinical studies. In the present study, we addressed the problem of unstable FFR signals by utilizing a stent-stabilization technique, in which the coronary artery adaptation process was impaired by a previously implanted self-apposing Stentys stent. This ensured that the balloon/artery ratio was maintained at a constant level unperturbed by blood flow and vessel adaptation.

Study limitations

One potential limitation to extrapolating the results of this study to clinical practice may be the use of ventricular pacing, which may potentially disturb physiological hemodynamics. Nevertheless, routine clinical practice shows that FFR measurements in the setting of ventricular pacing may be considered valid. Moreover, it has been shown experimentally that ventricular stimulation does not significantly change FFR results [23]. Confirmatory studies using atrial pacing might help explore this issue. Another limitation of this study was the limited number of animals and patients, which implies a relatively small number of measurements; however, as mentioned in the statistical analysis, we were able to perform enough measurements to meet our prespecified power calculations. Nevertheless, these results should be verified in future larger studies. Future research could also investigate the role of the HR on FFR in measurements in the territory of the circumflex artery. Although the impact of the HR on resting indices such as Pd/Pa or iFR might be scientifically interesting, it was not possible to conduct these measurements as well because of the constant adenosine infusion.

Conclusions

The prominent role of FFR in guiding revascularization strategies in sCAD requires a thorough exploration of any potential factors that may alter the FFR results. The results of our study indicate that significant tachycardia might be responsible for an overestimation of the FFR results in the LAD but not the RCA.

Impact on daily practice

These results have the potential to substantially affect clinical practice, especially regarding clinical decision-making when FFR values are borderline. It should be taken into consideration to recommend additional verification of borderline FFR results that were achieved at a higher

than average HR. The ANOVA analysis shows that differences increase with HR, they become clinically significant for high HRs, when in most cases FFR should not be performed. It is an open clinical question whether those correlations would be present in resting pressure indices such as iFR or rFR.

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Figure legends

Figure 1: Correlation of the HR and FFR in the porcine and human RCA and LAD.

The results of the FFR measurements in the porcine model of stent stabilized, balloon-narrowed RCA (A) and LAD (B) with the increasing HR beginning from the resting HR to pacing at 180 beats/minute. FFR assessment of moderate lesions in the RCA (C) and LAD (D) with the increasing HR, beginning from the resting HR to pacing at 160 beats/minute. The measurements were repeated at least 3 times for each HR. Because of the limited accuracy of FFR system ±0,01, results doubled or even tripled in some cases. Those HRs are represented by less than 3 FFR points on graphs A-D.

Figure 2: Average FFR in the human RCA and LAD

Average FFR results in angiographically moderate lesions in the RCA (A) and LAD (B) with the increasing HR beginning from the resting HR to pacing at 160 beats/minute. Post hoc analysis for LAD: *** $p<0,0001$; ** $p<0,001$; * $p<0,05$.

Table 1. The average FFR measurements in the porcine and human LAD and RCA during gradually elevated pacing rates

PORCINE MODEL				
	LAD		RCA	
	Mean HR (±SD)	Mean FFR (±SD)	Mean HR (±SD)	Mean FFR (±SD)
Without pacing	86.8±7.5	0.713±0.031	108.7±2.1	0.690±0.020
Pacing 110	110±0	0.770±0.010	-	-
Pacing 130	130±0	0.846±0.039	130±0	0.735±0.013
Pacing 140-150	142±4.5	0.868±0.062	150±0	0.707±0.006
Pacing 170-180	170±0	0.96±0	180±0	0.695±0.013
CLINICAL SETTINGS				
	LAD		RCA	
	Mean HR (±SD)	Mean FFR (±SD)	Mean HR (±SD)	Mean FFR (±SD)
Without pacing	59.2±5.9	0.814±0.057	65.2±6.8	0.881±0.055
Pacing 100	100±0	0.833±0.044	100±0	0.895±0.068
Pacing 130	130±0	0.851±0.046	130±0	0.901±0.076
Pacing 160	160±0	0.890±0.023	160±0	0.910±0.078

Table 2: Baseline clinical and demographic data. Data are given as median and IQR for continuous parametric data and n (%) for categorical data. LAD: left anterior descending artery, RCA: right coronary artery, significance level p<0,05.

	LAD (n=5)	RCA (n=4)	p
Age (years)	67 (66-68)	60 (54-63.5)	0.03
Ejection fraction of the left ventricle (%)	56 (46-57)	60 (57.5-62.5)	0.3 (ns.)
Lesion severity assessed by quantitative coronary angiography (%)	70 (70-80)	70 (70-75)	0.2 (ns.)
Male sex	5 (100%)	2 (50%)	0.2 (ns.)
Hyperlipidemia	4 (80%)	4 (100%)	1.0 (ns.)
Hypertension	4 (80%)	4 (100%)	1.0 (ns.)
Smoking	1 (20%)	1 (25%)	1.0 (ns.)
Diabetes mellitus	2 (40%)	0 (0%)	0.4 (ns.)
Implanted pacemaker	3 (60%)	0 (0%)	0.2 (ns.)
Atrial fibrillation	1 (20%)	0	1.0 (ns.)

Credit Author Statement

Przemysław J. Kwasiborski: Conceptualization, Methodology, Investigation, Writing - Original Draft **Wojciech Czerwiński:** Investigation **Paweł Kowalczyk:** Investigation**,** Software **Małgorzata Buksińska-Lisik:** Writing - Original Draft **Grzegorz Horszczaruk:** Investigation **Michael S. Aboodi:** Writing - Review & Editing **Kamil Derbisz:** Validation **Mariusz Hochul:** Investigation**; Adam Janas:** Investigation **Andrzej Cwetsch:** Supervision **Wojciech Wąsek:** Methodology **Piotr P. Buszman:** Funding acquisition**,** Investigation **Jozef Bartunek:** Writing - Review & Editing **Paweł E. Buszman:** Funding acquisition **Patrick W. Serruys:** Supervision**,** Writing - Review & Editing**, Krzysztof Milewski:** Supervision**,** Project administration, Funding acquisition

Highlights

- The correlation between FFR and HR was confirmed in a left anterior descending artery.
- In a right coronary artery the FFR was not biased by elevated HR.
- Significantly elevated HR may be responsible for an overestimation of FFR in LAD lesions.