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Effect of Systemic Arterial Blood Pressure on Fractional Flow Reserve

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Abstract

Backgraund: Fractional flow reserve (FFR) measures the flow reserve of narrowed coronary arteries. It is calculated simply as the ratio of hyperemic distal coronary pressure (Pd) to aortic pressure (Pa) (Pd/Pa). We aimed to examine the relationship between arterial blood pressure normalization and FFR in hypertensive patients.

Methods: Twenty patients (14 males, 6 females; age 62.7±6.1 years) who underwent coronary angiography (CAG) with a diagnosis of stable coronary artery disease (CAD), and had 50–70% stenosis in their coronary arteries and a blood pressure higher than 140/90 mmHg in the catheter laboratory, were included in this study. The total number of lesions studied was 20. FFR was measured using a pressure measurement wire from Certus (St. Jude Medical, St. Paul, MN, USA). Measurements were made with 150 mcg adenosine in the left anterior descending (LAD) and circumflex (Cx) arteries and 100 mcg in the right coronary artery (RCA). A FFR <0.80 was considered significant in both measurements, which were repeated after blood pressure normalization with nitroglycerin infusion at 20 mcg/min. The difference between the measurements [nitrate (-), nitrate (+]) was analyzed.

Results: Of the 20 lesions evaluated, 1 was in the left main coronary artery, 9 in the LAD, 6 in the Cx, and 4 in the RCA) Systolic, diastolic and mean blood pressure decreased significantly after nitroglycerin infusion (p <0.0001). There was no significant difference between nitrate (-) and nitrate (+) in baseline FFR measurements (p <0.084). There was a significant difference between nitrate (-) and nitrate (+) patients in FFR measurements after hyperemia (p <0.005). In two patients with significant FFR measurements prior to nitrate, FFR lost its significance after a blood pressure decrease following nitrate infusion.

Conclusion: In hypertensive individuals, hyperemia-related FFR values are significantly increased after normalization of blood pressure. In the evaluation of moderate coronary lesions of hypertensive patients with FFR, decreasing the mean blood pressure to normal values may be important for preventing unnecessary interventions.

Keywords: Arterial hypertension; Fractional flow reserve

Abbreviations: FFR: Fractional Flow Reserve; **IC**: Intracoronary; **IV**: Intravenous; **LV**: Left Ventricular; **Pa**: Systemic Aortic Pressure; **Pd**: Distal Coronary Pressure; **N+**: Nitrate Infusion +; **N-**: Nitrate Infusion -; **CAG:** Coronary Angiography

Introduction

The invasive management of coronary artery disease (CAD) requires both anatomical and functional assessment [1,2]. The association between angiographic coronary stenosis and the ischemic potential of a stenosis is quite complex and cannot be precisely determined by visual angiographic assessment alone. Therefore, the functional assessment of coronary physiology using intracoronary (IC) flow and pressure measurements has emerged as a pivotal adjunctive measure to determine the ischemic significance of a stenotic coronary lesion, and to assist in the final decision-making process.

Fractional flow reserve (FFR) evaluates the functional impact of a stenotic coronary lesion, and a threshold value of 0.75 corresponds to a significant stenosis. Due to a limited gray zone, an FFR ≤0.80 is the accepted threshold value for revascularization therapy [3,4]. Compared to visual angiographic evaluation, FFR is associated with a better prognosis in revascularization therapy [5]. Its reliability and simplicity of implementation make it an essential clinical tool for diagnostic coronary angiography (CAG); it is recommended in the absence of a prior non-invasive examination [6]. Although FFR, which is a method based on pressure measurement under maximal hyperemia, is accepted to be independent of hemodynamic parameters, such as heart rate and systemic blood pressure [7-10], previous theoretical studies have suggested that pressure-based FFR may be affected by changes in hemodynamic parameters, particularly absolute central aortic pressure [11].

Considering the direct therapeutic effect of FFR, and that wide inter-subject hemodynamic variation may be observed during coronary catheterization, the current study aimed to evaluate variations in FFR measurement in cases of arterial hypertension at the time of coronary angiographic assessment.

Methods

Study population

The present study was a single-center prospective study that included hypertensive patients with stable CAD and high blood pressure and a single *de novo* lesion in a coronary artery established for elective percutaneous coronary intervention. Ethical approval was obtained from the Ethics and Research Committee of our hospital. All participants provided written informed consent

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prior to enrolling in the study. The research was conducted in accordance with the principles of the Declaration of Helsinki. Regardless of past medical history, the diagnosis of hypertension was established if the systolic blood pressure was >140 mmHg or the diastolic blood pressure was >90 mmHg, as confirmed by invasive measurements during the procedure in the catheter laboratory. Patients with low or normal blood pressure during the procedure, diffuse or three vessel CAD, left ventricular ejection fraction <50, severe valvular pathology, prior cardiac surgery, left ventricular (LV) hypertrophy, cardiac arrhythmia, coronary ectasia, coronary slow flow, acute coronary syndrome, abnormal clotting profiles and impaired kidney function with creatinine >1.5mg/dl were excluded from this study.

Coronary angiography and FFR measurement

The CAG was performed by a femoral approach with 1 mg of IC nitrate in cases of CAD. Angiographic images of the stenotic coronary lesion were analyzed visually and quantitatively (Centricity® CA1000; GE Healthcare, Little Chalfont, Buckinghamshire, UK). FFR was measured when clinically indicated using a 6Fr catheter after oral 300mg acetylsalicylic acid and intravenous (I.V.) injection of 5,000IU unfractionated heparin. A 0.014" PressureWire Certus (St. Jude Medical, St. Paul, MN, USA) was calibrated and then passed through the stenotic lesion. Hyperemia was provided by IC injection of adenosine (150µg of adenosine for the left anterior descending (LAD) and circumflex (Cx) artery lesions, 100 µg of adenosine for the right coronary artery (RCA) lesions) ahead of the baseline FFR measurement (FFR1). Curve equalization was regularly checked at the end of the procedure upon withdrawal of the FFR wire.

After baseline FFR measurements (FFR_1) of hypertensive patients, 20µcg/kg/min nitroglycerin infusion was administered I.V. Approximately 10min later, FFR measurements (FFR_2) (both basal and adenosine hyperemic) were repeated in patients whose systemic blood pressure regressed to normal limits. The mean arterial pressure was not reduced to below 70 mmHg in any patient. Hypertensive (FFR_1) and normotensive (FFR_2) measurements were compared. Adenosine was administered to patients to ensure distal hyperemia and reduce the blood pressure of patients to a normal range by applying nitrate infusion. Adenosine-induced bradyarrhythmia was not observed during the FFR application procedure, but hypotension developed during Nitroglycerin infusion in two patients. Discontinuing nitrate infusion was sufficient for patients with reduced blood pressure. After Nitroglycerin infusion measurements of all patients were performed when the patient's blood pressure values were within the normal range.

Statistical Analysis

As descriptive statistics, mean, standard deviation, median lowest, highest, frequency, and ratio values were calculated. The distribution of the variables was measured with the Kolmogorov-Smirnov test. The Wilcoxon test was used to analyze dependent quantitative variables. Spearman correlation analysis was used for correlation analysis. SPSS software (ver. 22.0; SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

We examined FFR in 20 of 323 consecutive patients with an intermediate coronary stenosis (6.1%) who underwent CAG. There were 14 male and 6 female patients. The mean age was 62.7 ± 6.1 years. A total of 20 lesions (9 LAD, 6 CX, 4 RCA, and 1 left main coronary artery) were examined. Clinical and angiographic data are presented in Table 1.

Discontinuing Nitroglycerin infusion was sufficient for patients with reduced blood pressure. After Nitroglycerin infusion measurements of all patients were performed when the patient's blood pressure values were within the normal range. After nitrate infusion, the heart rate was in the normal range, with a statistically significant increase ($p < 0.05$). After nitrate infusion, systolic blood pressure decreased significantly ($p < 0.05$) and diastolic blood pressure also showed a significant decrease ($p < 0.05$). The mean blood pressure after nitrate infusion decreased significantly ($p < 0.05$) compared to the pre-nitrate levels. There was a significant difference between hypertensive and normotensive FFR measurements after hyperemia ($p < 0.005$). Baseline measurements after nitrate infusion showed no significant change ($p > 0.084$) (Table 2).

In two hypertensive patients with significant FFR measurements before nitrate (FFR <0.80), FFR lost statistical significance after their blood pressure decreased to the normal range (Figures 1, 2 and 3).

There was no significant correlation observed between mean arterial pressure and FFR before nitrate infusion (r=0.326/p=0.161).

Discussion

We found that FFR values may increase following normalization of blood

Table 1. Demographic, clinical, and angiographic characteristics of the study population.

Variables		Min-Max	Median	Mean ± s.d./n-%	
Age		55 - 76	62	62.7 ± 6.1	
Gender	Female	--	--	6	30.0%
	Male	--	--	14	70.0%
DM	--	--	--	8	40.0%
HT	--	--	--	8	40.0%
HLP	--	--	--	7	35.0%
Family history	--	--	--	13	65.0%
Smoking	--	--	--	11	55.0%
LMCA	--	--	--	1	5.0%
LAD	--	--	--	9	45.0%
Cx	--	--	--	6	30.0%
RCA	--	--	--	4	20.0%
Stenosis Severity (% - Visual Assessment)	--	50 - 60	53	54.3 ± 4.7	
Stenosis Severity (% -Quantitative Assessment)	--	45 - 65	54	54.4 ± 6.1	
Stenotic Segment Length (Mm)	--	4.0 - 35.0	18.0	18.0 ± 7.8	
Coronary Artery Diameter (Mm)	--	2.5 - 5.0	3.0	3.2 ± 0.6	

LMCA: Left Main Coronary Artery
LAD: Left Anterior Descending Coronary Artery
Cx: Circumflex Coronary Artery
RCA: Right Coronary Artery
s.d.: Standard Deviation

Table 2. Haemodynamics and FFR variations.

Variables		Min-Max	Median	Mean ± s.d.	p-value
Heart Rate	Nitrate (-)	68.0 - 80.0	75.5	74.9 ± 2.9	0.000w
	Nitrate (+)	79.0 - 93.0	86.0	86.5 ± 3.8	0.000w
Sistolic Blood Pressure	Nitrate (-)	130.0 - 180.0	159.5	155.9 ± 14.6	0.000w
	Nitrate (+)	107.0 - 155.0	117.5	121.7 ± 13.3	0.000w
Diastolic Blood Pressure	Nitrate (-)	70.0 - 115.0	96.5	94.5 ± 12.3	0.000w
	Nitrate (+)	55.0 - 95.0	75.0	73.8 ± 11.6	0.000w
Mean Blood Pressure	Nitrate (-)	93.0 - 133.0	117.5	115.1 ± 11.2	0.000w
	Nitrate (+)	72.0 - 115.0	90.0	89.3 ± 11.2	0.000w
Baseline Measurement	Nitrate (-)	0.9 - 1.0	1.0	10 ± 0.0	0.000w
	Nitrate (+)	0.9 - 1.0	1.0	10 ± 0.0	0.000w
Post-Adenosine Measurement	Nitrate (-)	0.7 - 1.0	0.9	0.8 ± 0.1	0.084w
	Nitrate (+)	0.8 - 1.0	0.9	0.9 ± 0.1	0.000w

w: Wilcoxon test; * Results Before Adenosine Administration; ** Results After Adenosine Administration

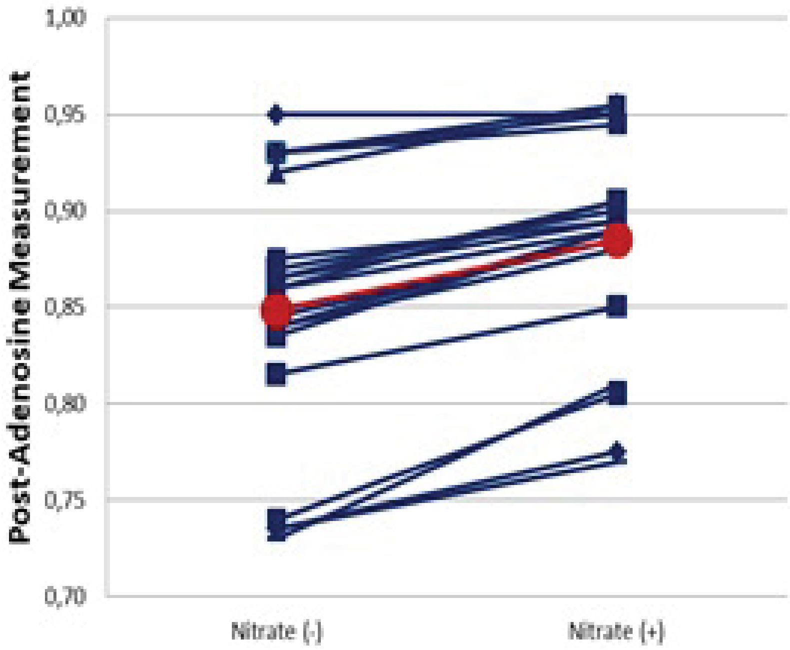

Figure 1. Changes in FFR values with intravenosus nitroglycerine administration.

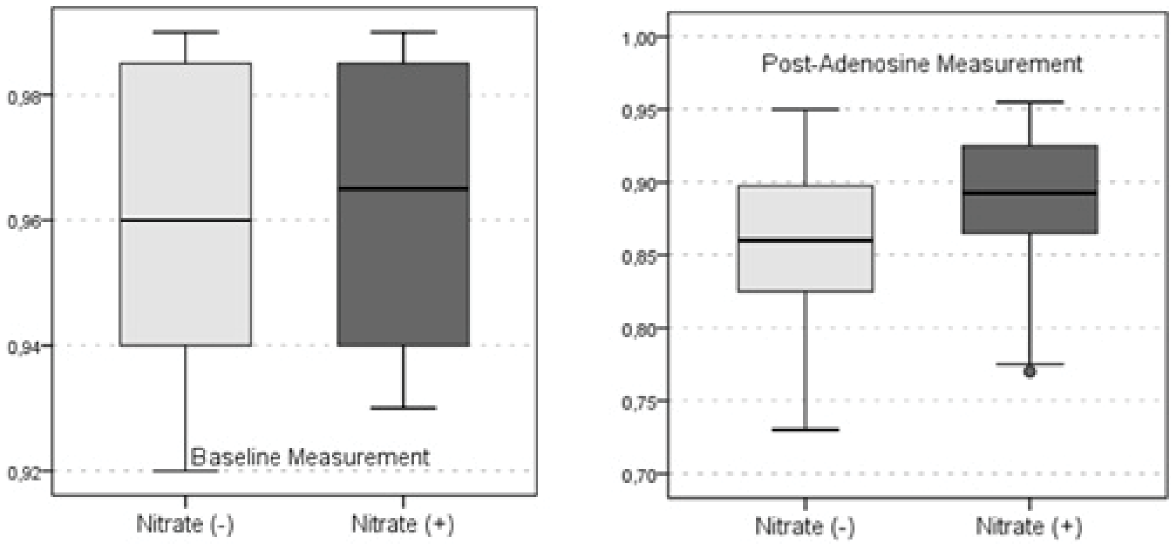

Figure 2. FFR results before adenosine administration (left one), FFR results after adenosine administration (right one).

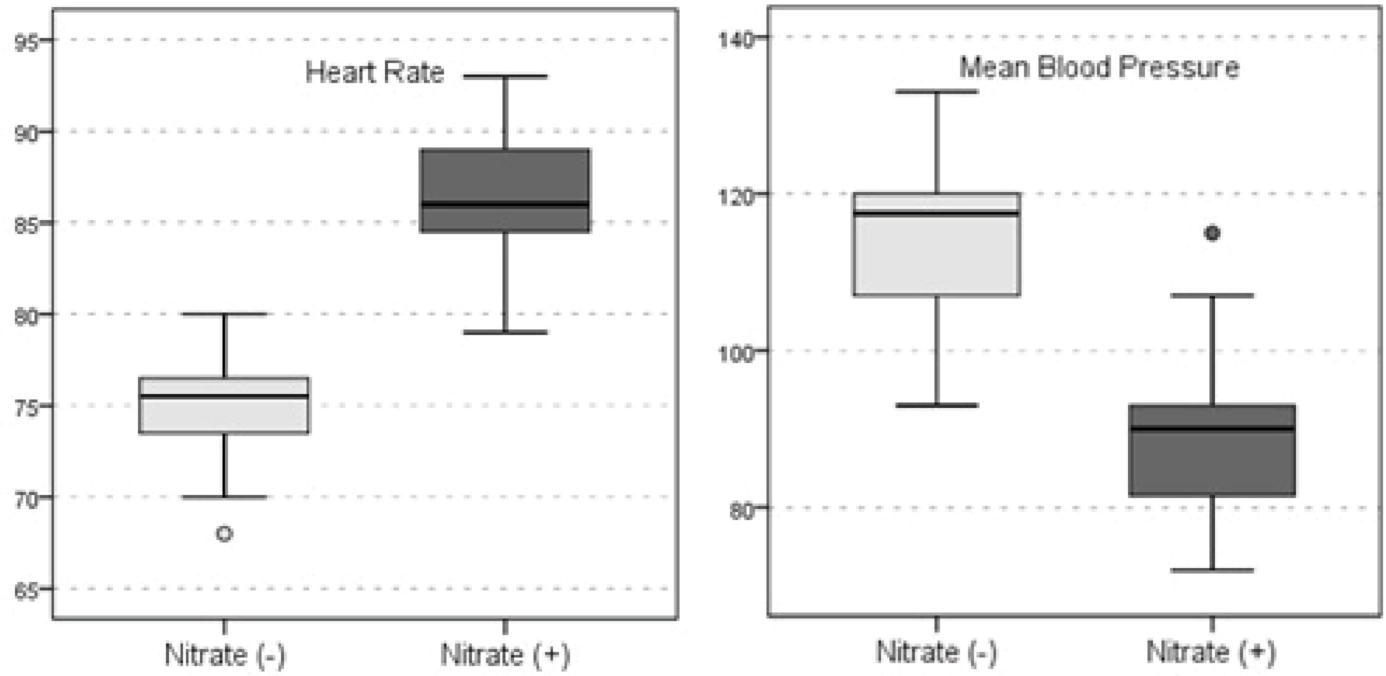

Figure 3. Change in heart rate with intravenous nitroglycerin administration (left one), change in mean blood pressure with intravenous nitroglycerin administration.

pressure in patients with CAD and hypertension. This observational study confirms the *in vitro* modeling data. Moreover, the results of this study raise the issue of the independence of FFR with respect to systemic blood pressure in a borderline condition.

Current data suggest that the decision for coronary revascularization should be reached according to the physiological ischemia caused by the lesion, not by the angiographic percentage of stenosis [12,13]. For this reason, the FFR procedure, which is based on pressure measurement, is one of the most appropriate options for evaluating ischemia when deciding on revascularization. Tarkin et al. recently reported a large retrospective analysis of coronary angiographic data and studied the hemodynamic response of I.V. adenosine, and its impacts on coronary and systemic blood pressure and FFR [14]. In this prospective study of intermediate stenosis, proximal pressure of stenosis (P_a) was responsible for the majority of the fall in the distal pressure of the stenosis (P_d). Furthermore, when there is a major fall in Pa, the obvious fall in the P_d/P_a measurement may not indicate worsening stenosis; it may be mostly due to the lower Pa and P_d values. Moreover, in this clinical study, I.V. adenosine resulted in alterations in systemic blood pressure, which may lead to changes in FFR lesion classification, potentially impacting clinical management decisions [14]. Consistent with these clinical data, the results of our study also showed variation in FFR with arterial pressure. The FFR values of hypertensive patients improved following normalization of blood pressure (from hypertensive to normotensive). Four of our patients' FFR values showed clinically significant stenosis of the vessel while the blood pressure was high; however, their FFR values improved after I.V. nitrate administration. Moreover, IC adenosine-induced hyperemia improves FFR values far more than I.V. nitrate administration alone, thus decreasing blood pressure.

FFR is believed to be independent of hemodynamic conditions [15], but FFR may vary by approximately 4% with changes in blood pressure [1]. De Byrune et al. performed FFR studies in humans and reduced arterial pressure by nitroprusside infusion. After infusion, they found a variation of 3.3% in FFR values with Pa changes. In severe stenosis, this variation increased 2-fold. They reduced the mean blood pressure from 100 ± 6 mmHg to 79 ± 6 mmHg. Significant reflex tachycardia due to nitroprusside likely affected coronary flow and the distal coronary pressure (Pd)/aortic pressure (Pa) ratio (Pd/Pa) [14]. In the present study, reflex tachycardia occurred after nitrate infusion, but the heart rate remained within the normal range. However, both blood pressure decrease and heart rate increase may have contributed in this result.

Siebes et al. showed that blood pressure changes have a clear effect on FFR measurements. They also showed that FFR increased with a decrease in Pa. The sensitivity of FFR to these hemodynamic changes was highest for stenoses of intermediate severity [11]. In the current study, a significant improvement was observed in the FFR values of all patients following normalization of systemic blood pressure, while in some cases, both statistically and clinically significant improvement in FFR values was observed. In other words, some coronary lesions were classified as severe stenosis when the systemic arterial pressure was higher, while the same lesions did not cause severe stenosis when systemic arterial pressure was normalized. These results suggest that FFR measurement should be performed on normotensive patients, and that FFR measurement is affected by systemic blood pressure.

Moreover, Claessens et al. stated that FFR values differed from Pa and corrected FFR values should be calculated in FFR studies performed by coronary modeling [16]. Together, these findings support the results of the current study.

Valerian et al. presented a hemodynamic study concluding that increasing LV diastolic pressure can increase FFR, particularly in patients with an FFR of 0.80 and low blood pressure [17]. Robert et al. showed that LV end diastolic pressure increased significantly in FFR measurements [12]. In our study, we did not measure LV end diastolic pressure, but it is possible that the end diastolic pressure may decrease due to nitroglycerine infusion. We hypothesized that nitroglycerine infusion could decrease LV end diastolic pressure and increase FFR measurements. In this respect, we believe that our study reached the same conclusion as the above studies.

Florence et al. repeated FFR measurements after blood pressure normalization by infusing phenylephrine into hypotensive patients and found significant changes in FFR values. Three patients with normal FFR values exhibited significant FFR values after blood pressure normalization [18]. Besides, a more recent study conducted by Karuta et al. assessed the effect of blood pressure (BP) on coronary computed tomography angiography (CTA) derived computational fractional flow reserve (CTA-FFR) and found a similar result to our study. They showed that BP variations in the common range may slightly affect CTA-FFR and BP assumptions could cause misinterpretation of borderline significant lesions [19].

In our study, we used I.V. nitroglycerin to decrease the blood pressure in hypertensive patients and evaluated the effect of blood pressure normalization on FFR. Our work is similar to that of Florence and colleagues. In both studies, after the blood pressure was normalized, the tests were repeated and similar results were found. We found that hyperemic FFR levels increased significantly after arterial pressure normalization. In two patients with significant FFR measurements obtained before nitrate infusion, FFR lost significance after the blood pressure decreased to a normal range.

Conclusion

Systemic arterial hypertension likely affects FFR measurements. In hypertensive patients with an intermediate coronary stenosis, FFR measurements may show coronary lesions as being physiological and more serious than they actually are. In hypertensive individuals, hyperemia-related FFR values are significantly improved by normalization (decrease) of the patient's blood pressure. Therefore, reducing the mean blood pressure to a normal range during FFR evaluation may be important for the prevention of unnecessary revascularization procedures for moderate coronary lesions.

Study Limitations

Our study had some limitations. First, it was an observational case-control study and we were not able to obtain complete follow-up data. Second, the number of patients was relatively small; thus, larger studies are needed to detect a causal relationship between systemic blood pressure and FFR measurements.

Ethical Standards

The authors assert that all procedures contributing to this study complied with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Authorship Contributions

Concept: Osman Kayapinar and Cem Ozde; design: Osman Kayapinar; supervision: Osman Kayapinar; resources: Cem Ozde materials: Cem Ozde, data collection and/or processing: Osman Kayapinar,Gülşah Aküre and Cem Ozde; analyses and/or interpretation: Osman Kayapinar, Adnan Kaya ; literature search: Osman Kayapinar; writing: Osman Kayapinar and Cem Ozde; critical review: Osman Kayapinar.

References

1. Levine Glenn and John Bittl. "Focused update on Primary Percutaneous Coronary Intervention for Patients with ST-Elevation Myocardial Infarction." *JAMA Cardiology* 1(2016): 226-227.
2. Windecker Stephan, Stefan Stortecky, Giulio Stefanini, Anne Rutjes, et al. "Revascularisation versus Medical Treatment in Patients with Stable Coronary Artery Disease: Network Meta-Analysis." *BMJ* 348 (2014).
3. Pijls Nico, Bernard Bruyne, Kathinka Peels, Pepijn van der Voort, et al. "Measurement of Fractional Flow Reserve to Assess the Functional Severity of Coronary-Artery Stenoses." *New England Journal of Medicine* 334(1996): 1703-1708.
4. Tonino Pim, Bernard De Bruyne, Nico Pijls, Uwe Siebert, et al. "Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention." *New England Journal of Medicine* 360(2009): 213-224.
5. Pijls Nico, William Fearon, Pim Tonino, Uwe Siebert, et al. "Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention in Patients with Multivessel Coronary Artery Disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) Study." *Journal of the American College of Cardiology* 56(2010): 177-184.
6. Patel Manesh, Gregory Dehmer, John Hirshfeld, Peter Smith et al. "ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 appropriate use Criteria for Coronary Revascularization Focused update: A Report of the American College of Cardiology Foundation appropriate use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, society of Thoracic Surgeons, American association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography." *Journal of the American College of Cardiology* 59(2012): 857-881.
7. Pijls Nico and Bernard de Bruyne. "Coronary pressure measurement and fractional flow Reserve." *Heart* 80(1998): 539-542.
8. Pijls Nico, Bernard de Bruyne, Kathinka Peels, Pepijn van der Voort, et al. "Measurement of Fractional Flow Reserve to Assess the Functional Severity of Coronary-Artery Stenoses." *New England Journal of Medicine* 334(1996): 1703-1708.
9. Bernard de Bruyne, Jozef Bartunek, Stanislas Sys, Nico Pijls, et al. "Simultaneous coronary Pressure and Flow Velocity Measurements in Humans: Feasibility, Reproducibility, and Hemodynamic Dependence of Coronary Flow Velocity Reserve, Hyperemic Flow versus Pressure Slope Index, and Fractional Flow Reserve." *Circulation* 94(1996): 1842-1849.
10. Pijls Nico, Morton Kern, Paul Yock and Bernard De Bruyne. "Practice and Potential Pitfalls of Coronary Pressure Measurement." *Catheterization and* Cardiovascular İnterventions 49(2000): 1-16.
11. Siebes Maria, Steven Chamuleau, Martijn Meuwissen, Jan Piek, et al. "Influence of Hemodynamic Conditions on Fractional Flow Reserve: Parametric Analysis of Underlying Model." *American Journal of Physiology-Heart and Circulatory Physiology* 283 (2002): 1462-1470.
12. Leonardi Robert, Jacob Townsend, Chetan Patel, Bethany Wolf, et al. "Left Ventricular End-Diastolic Pressure affects Measurement of Fractional Flow Reserve." *Cardiovascular Revascularization Medicine* 14(2013): 218-222.
13. Pijls Nico, Berry Gelder, Pepijn Voort, Kathinka Peels, et al. "Fractional Flow Reserve: A Useful Index to Evaluate the Influence of An Epicardial Coronary Stenosis on Myocardial Blood Flow." *Circulation* 92(1995): 3183-3193.
14. Tarkin Jason, Sukhjinder Nijjer, Sayan Sen, Ricardo Petraco, et al. "Hemodynamic Response to Intravenous Adenosine and its Effect on Fractional Flow Reserve Assessment: Results of the Adenosine for the Functional Evaluation of Coronary Stenosis Severity (AFFECTS) Study." *Circulation: Cardiovascular Interventions* 6(2013): 654-661.
15. Kern Morton, Amir Lerman, Jan-Willen Bech, Bernard De Bruyne, et al. "Physiological Assessment of Coronary Artery Disease in the Cardiac Catheterization Laboratory: A Scientific Statement from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology." *Circulation* 114(2006): 1321-1341.
16. Claessens Tom, Paul Herck, Koen Matthys, Patrick Segers, et al. "Influence of Zero Flow Pressure on Fractional Flow Reserve." *Biomechanics and modeling in Mechanobiology* 3(2004): 48-55.
17. Ryan TJ, Bauman WB, Kennedy JW, Kereiakes DJ, et al. "American Heart Association Task Force Report: Guidelines for Percutaneous Transluminal Coronary Angioplasty: A Report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Percutaneous Transluminal Coronary Angioplasty)." *J Am Coll Cardiol* 22(1993): 2033-2054.
18. Verdier-Watts Florence, Gilles Rioufol, Nathan Mewton, Ingrid Sanchez, et al. "Influence of Arterial Hypotension on Fractional Flow Reserve Measurements." *EuroIntervention* 11(2015): 416-420.
19. Kurata Akira, Adriaan Coenen, Marisa Lubbers, Koen Nieman, et al. "The Effect of Blood Pressure on Non-invasive Fractional Flow Reserve Derived from Coronary Computed Tomography Angiography." *European Radiology* 27(2017): 1416-1423.

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