Fractional Flow Reserve to Heart Rate Dependency in Different Epicardial Territories

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Introduction

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- Fractional flow reserve (FFR) measurement is considered as a gold standard in physiological assessment of coronary stenosis and is actually a decision making tool
- Coronary blood flow occurs primarily during diastole and drops nearly to zero during systole (de Bruyne, Bartunek et al. 1996) due to the high strain of the cardiac muscle that obstructs microcirculation
- Increased heart rate (HR) shortens the diastole and keeps the duration of systole relatively constant
- **Therefore we evaluated the relationship between FFR and HR** in the following experimental settings:

In silico model → Preclinical tests → Clinical test

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- In addition, we verified for the first time **if there is a difference in FFR and HR correlation between LAD and RCA**
- This is based on the assumption that systolic reduction of blood flow in RCA is much less evident than in LAD due to the low-pressure territory of right ventricle that is supplied by RCA

In silico model

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- Assuming that the coronary flow occurs only during diastole (de Bruyne, Bartunek et al. 1996) and each HR increase is realized mostly by shortening the diastole (Cui, Roberson et al. 2008) it was possible to elaborate **mathematical formula of FFR and HR dependency and prepare model of linear regression**

- *To estimate the upper limit of HR impact on FFR it was assumed that the flow during systole is stopped, in terms of pressures it means that Pa=Pd and that implies FFR systole =1. Each deviation from this assumption reduces potential HR influence on FFR value.*
  - *Duration of systole in ms – 435,13-1,43*HR (Cui, Roberson et al. 2008)*
  - *Duration of diastole in ms – 1428-16,6HR+0,05HR2. (Cui, Roberson et al. 2008)*

$$FFR = FFR_{systole}\frac{435,13 - 1,43 * HR}{60 * 1000}HR + FFR_{diastole}\left(\frac{1428 - 16,6HR + 0,05HR^2}{1000 * 60}\right)HR$$

$$FFR = \frac{435,13-1,43*HR}{60*1000}HR + FFR_{diastole}\left(\frac{1428-16,6HR+0,05HR^2}{1000*60}\right)HR$$

In silico model

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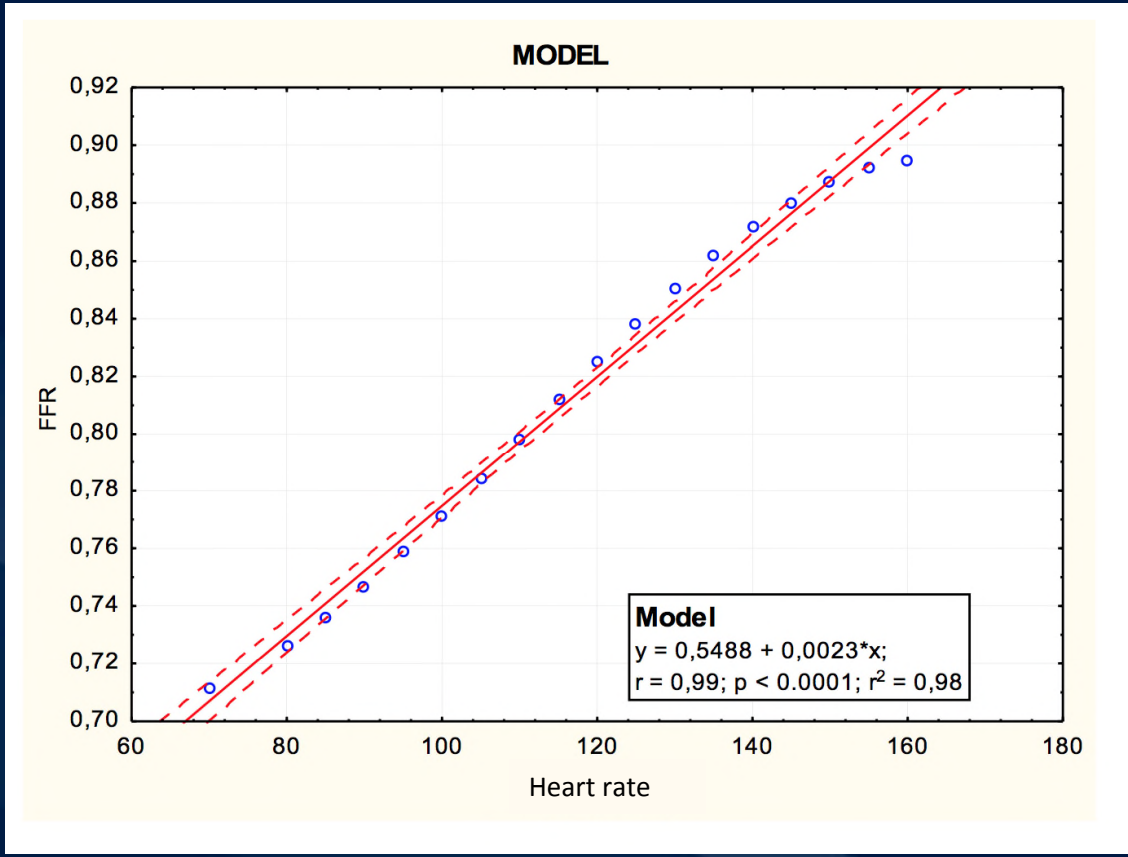
Model of linear regression that theoretically predicts HR impact on FFR value at HR range 60-180 beats per minute = positive correlation between FFR and HR



The formula was than verified experimentally

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Preclinical part

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- The study protocol approved by the local ethics committee
- 4 domestic pigs (weight 72±5,3 kg) were included in the study
- Cardiac catheterization performed through standard femoral access with the use of 6F right and left Judkins catheters
- Pacing electrode introduced to the right ventricle through 7F sheath in femoral vein
- After diagnostic angiography 3.0-3.5 mm STENTYS stents were implanted in the mid-portions of right (RCA) and left descending arteries (LAD) respectively (avoiding side branches) to block physiological adaptations of the artery

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Preclinical part

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- **Artificial stenosis** to achieve FFR in a range between 0.7 - 0.8 was achieved by controlled NC balloon inflation within previously implanted stent under full hyperemia (intravenous infusion of 140 ug/kg of adenosine)
- Previously inflated balloon was kept in the artery five minutes before any measurements
- Pacing was incremented each time by 20 beats/minute and 3 FFR measurements were registered with the same protocol, up to 180 beats per minute
- In total **33 FFR measurements were done (14 RCA and LAD 19)**

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Results of preclinical study

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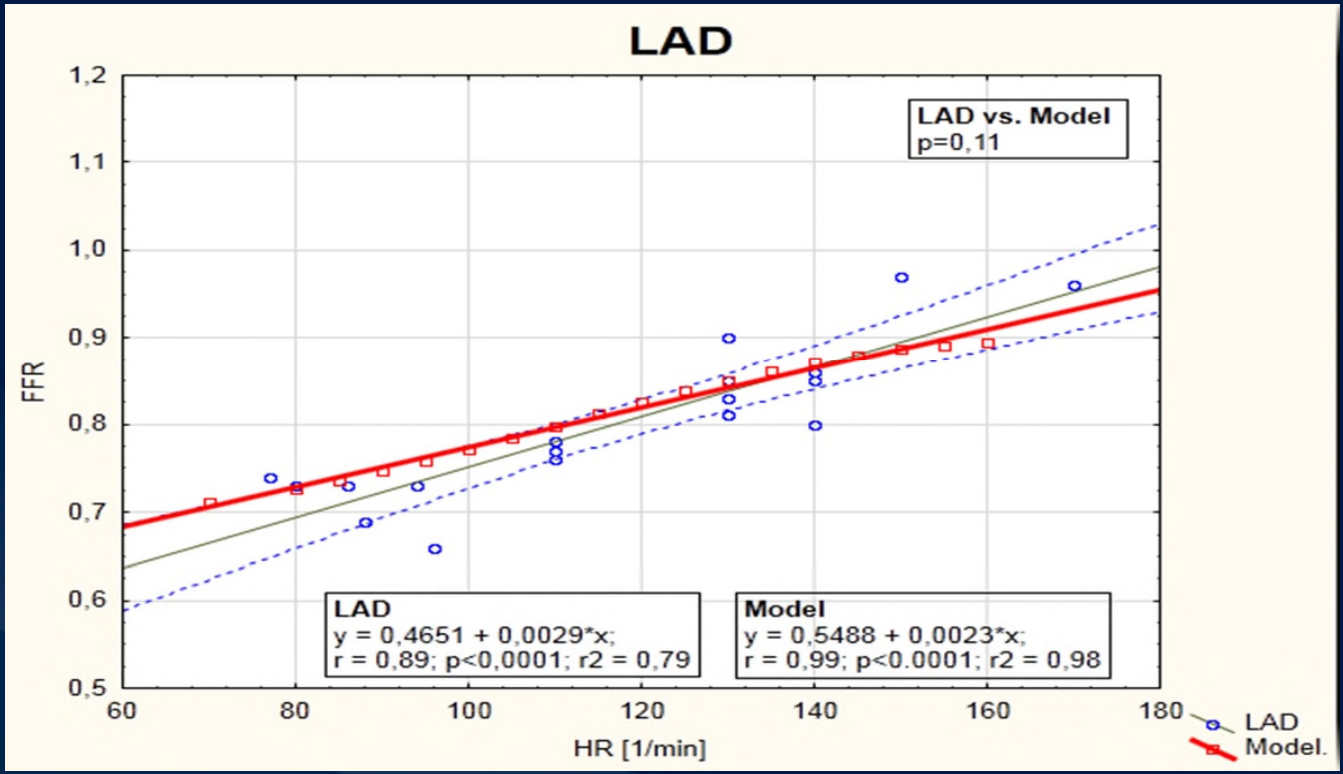

Presented results indicate **strong, positive correlation between FFR and HR in LAD** (r2 =0,79, p<0,0001). Moreover it was shown that the deviation from model prediction is not significant (p=0,11).

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Pearson correlation; p value ≤0,05 as significant

Results of preclinical study

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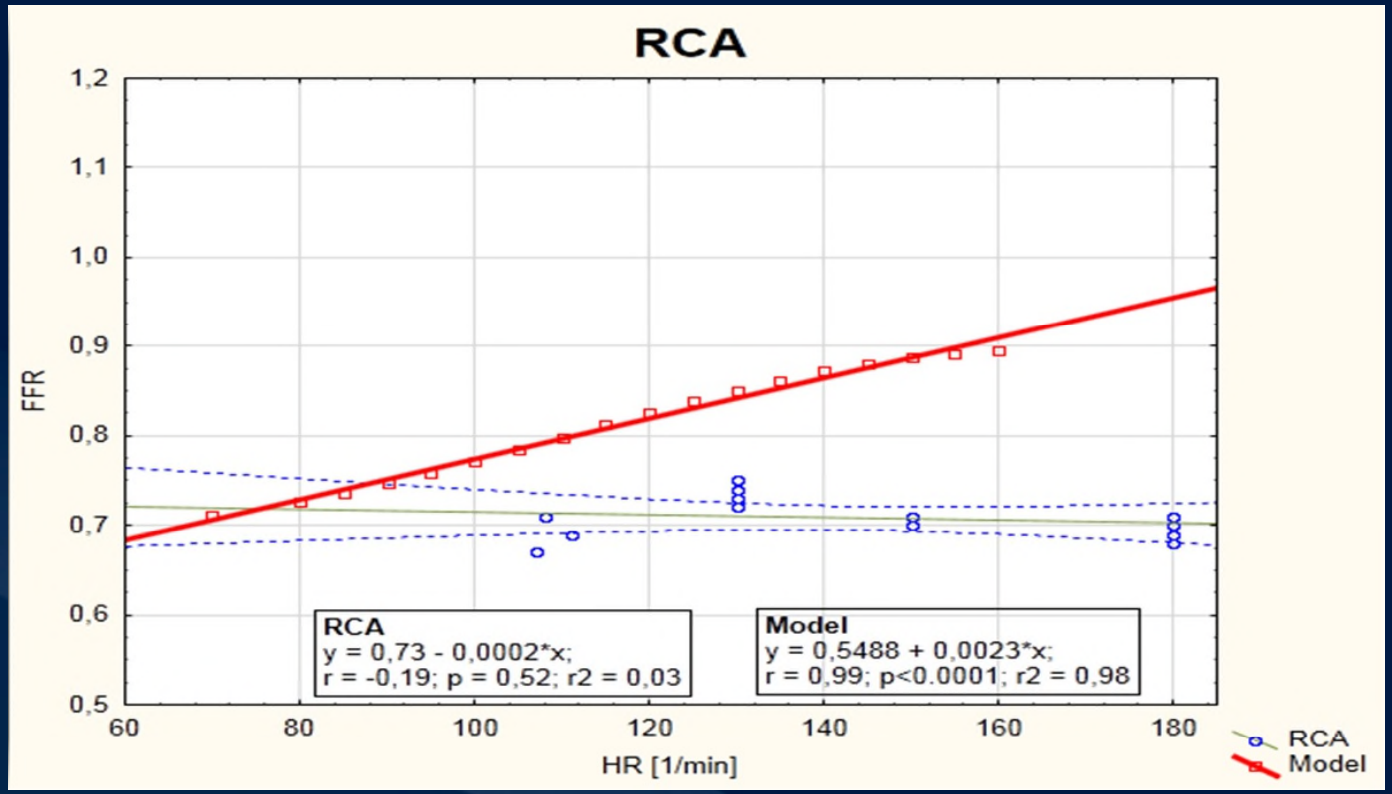

There is **no significant correlation between HR and FFR in RCA** (r2=0,03, p=0,52)

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Clinical part

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- Patients (≥ 18 ≤ 85 years old) presenting symptoms of stable CAD and borderline lesions in LAD or RCA (%DS between 40-70% by visual estimate)
- The baseline value of FFR <0.80
- Pacing electrode introduction into the right ventricle (only in the absence of previously implanted pacemaker)
- 3 FFR measurements performed after maximum hyperemia (adenosine 140ug/kg)
- Pacing was incremented each time by 20 beats/minute and 3 FFR measurements were registered up to 160 beats per minute
- **In total 105 FFR measurements were done (48 in RCA and LAD 57)**

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Clinical part

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- **Inclusion criteria:**
  - Planned admission to invasive coronary angiography
  - Age ≥ 18 ≤ 85 years old
  - The value of FFR <0.80
- **Exclusion criteria:**
  - Heart failure, ef ≤35%
  - Inability of cardiac stimulation
  - Active malignant neoplasm
  - Active tuberculosis, viral hepatitis, liver failure
  - Poor controlled diabetes (HbA1c>8%)
  - Chronic kidney disease (eGFR <45ml/min/1,73m^2)
  - Asthma, COPD
  - Recent stroke, severe hypertension

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Clinical study: patients baseline

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VARIABLE	LAD n=5 (MEAN±SD)	RCA n=4 (MEAN±SD)	P
AGE	68±3,5	59±6,5	0,03
EF (%)	53,8±8,3	60±4,1	0,3
STENOSIS (%)	74±5,5	72,5±5	0,2
SEX	♂ 5 ♀ 0	♂ 2 ♀ 2	0,2
HYPERLIPIDEMIA	80% (n=4)	100% (n=4)	1
HYPERTENSION	80% (n=4)	100% (n=4)	1
MYCORADIAL INFARCTION	40% (n=2)	100% (n=4)	0,2
DIABETES	40% (n=2)	0	0,4
CARDIAC STIMULATOR	60% (n=3)	0	0,2

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Results of clinical study

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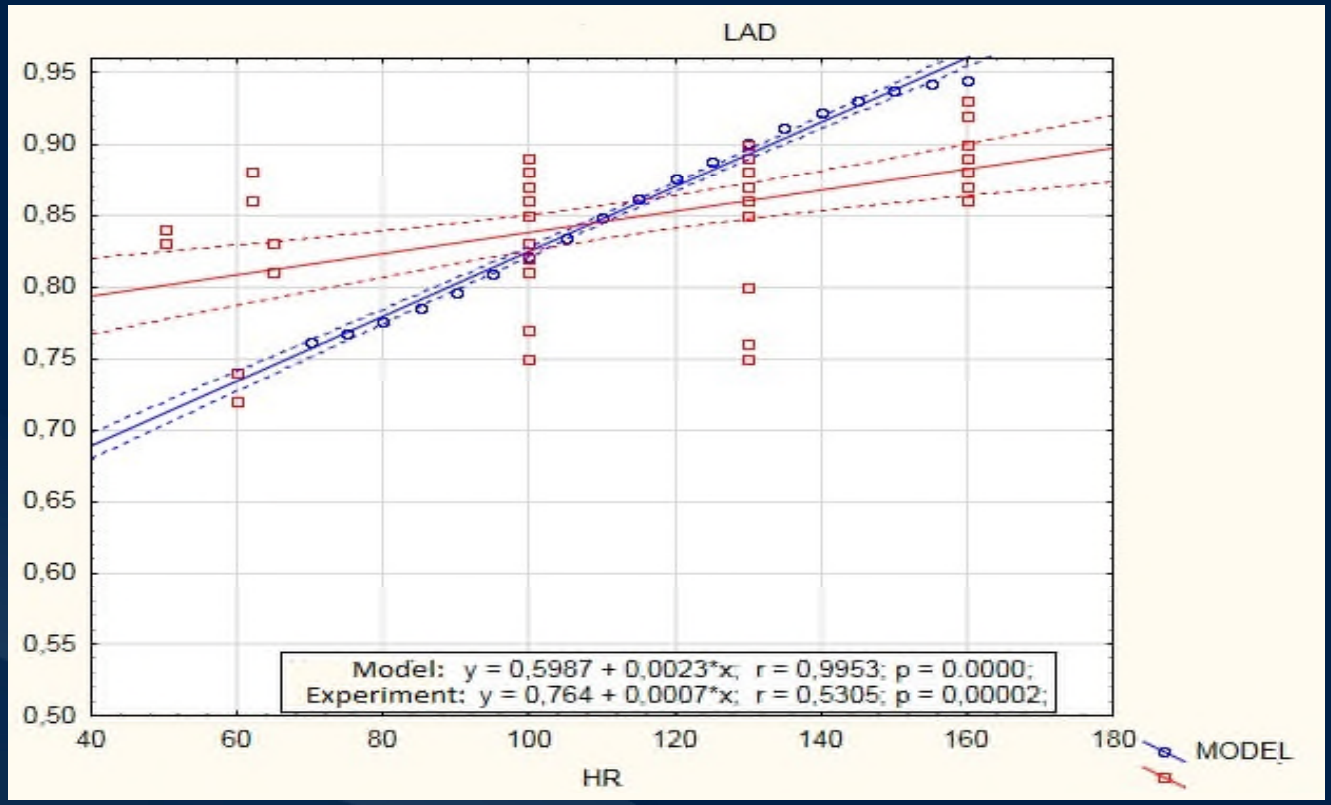

Clinical tests **confirmed finding of preclinical study** indicating **strong, positive correlation between FFR and HR in LAD** (r2 =0,53, p=0,00002). Deviation form model prediction was not significant (p=ns)

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Results of clinical study

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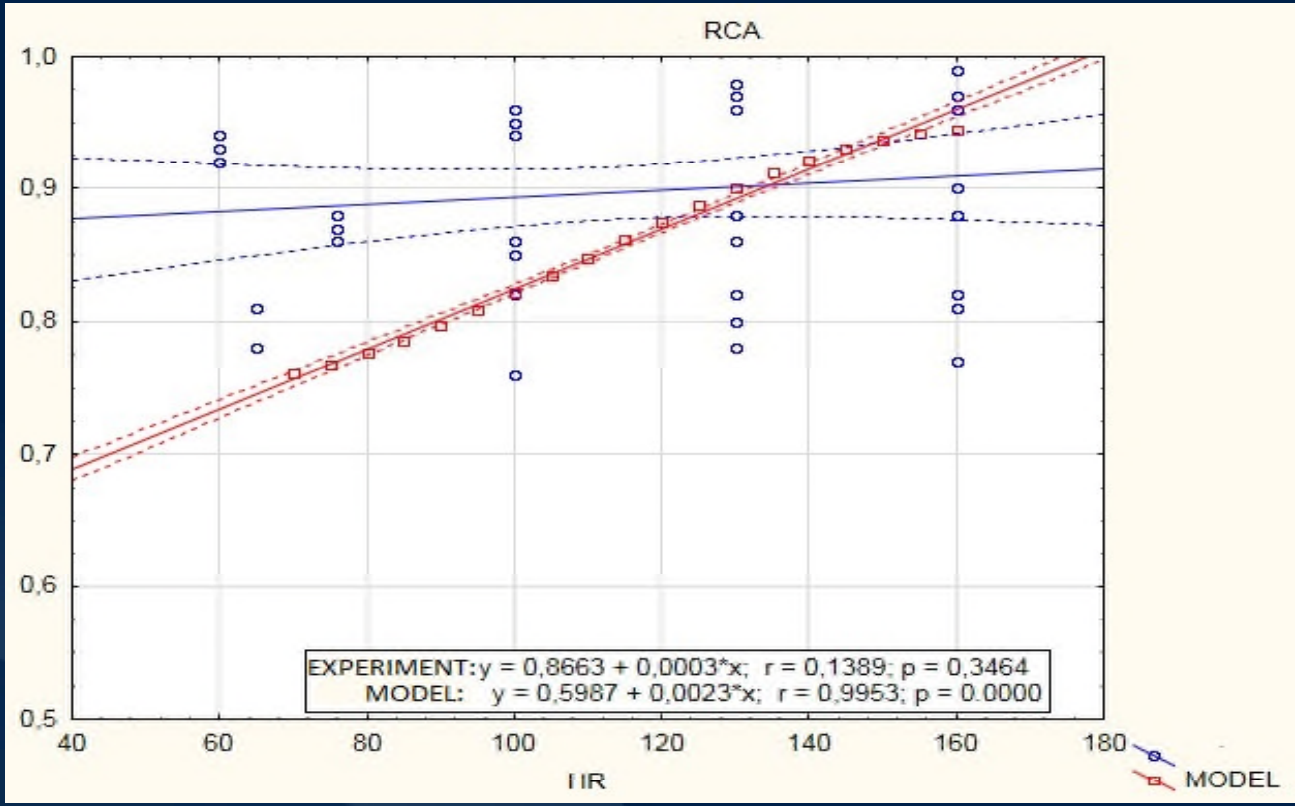

Similarly to preclinical settings there was **no significant correlation between HR and FFR in RCA** (p=0,34)

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Discussion

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- **Lack of correlation between FFR and HR found in RCA** seems to be related to the different coronary flow pattern as compared to LAD
- The systolic reduction of blood flow in RCA is much less evident due to the low-pressure territory of right ventricle that is supplied by RCA

Discussion

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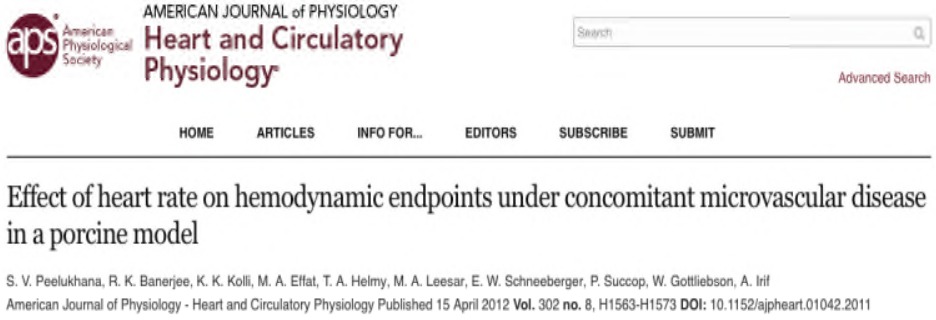
- **2 previous experimental studies did not confirm HR influence on FFR:**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Influence of heart rate on fractional flow reserve, pressure drop coefficient, and lesion flow coefficient for epicardial coronary stenosis in a porcine model

Kranthi K. Kolli, R. K. Banerjee, Srikara V. Peelukhana, T. A. Helmy, M. A. Leesar, Imran Arif, E. W. Schneeberger, Dwight Hand, Paul Succop, W. M. Gottliebson, M. A. Effat

American Journal of Physiology - Heart and Circulatory Physiology Published 1 January 2011 **Vol.** 300 **no.** 1, H382-H387 **DOI:** 10.1152/ajpheart.00412.2010

- Lesions were created by controlled balloon inflation in normal, healthy arteries that are exposed to constant physiological adaptation mechanisms
- Balloon inflated in healthy, adapting artery won't create functionally stable lesion
- In Peelukhana paper, FFR measurements varied from 0.3 to nearly 1.0 (at the same HR and with the same balloon)
- Lack of functionally stable lesion might be the cause of poor correlation between HR and FFR

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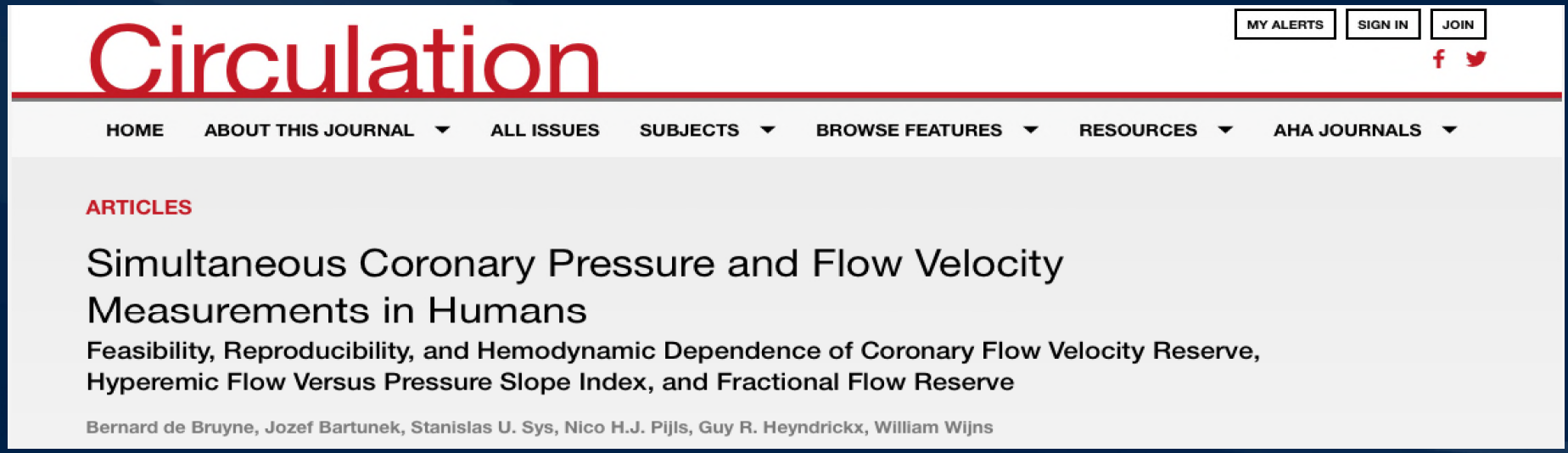
- **Only one study performed on humans** (de Bruyne, Bartunek et al. 1996) on relatively small group of subjects and **without artery separation** - all lesions in different arteries were analyzed together
- In this study the FFR was measured for **relatively narrow range of HR (80-110)** which might be another cause of negative result



Conclusions

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- The results indicate that interventional cardiologist should be aware of patient HR during FFR measurements in LAD as **high HR might be responsible for false negative FFR measurements**
- Further observations may be required in order to consider implementation of correction coefficient to normalize FFR results in LAD achieved at different HR values