

VU Research Portal

Combined flow and pressure measurements in coronary artery disease

Marques, K.M.J.

2008

document version

Publisher's PDF, also known as Version of record

[Link to publication in VU Research Portal](#)

citation for published version (APA)

Marques, K. M. J. (2008). *Combined flow and pressure measurements in coronary artery disease*.

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:

vuresearchportal.ub@vu.nl

Summary

In the catheterization laboratory, the cardiologist often is faced with the problem to indicate among many coronary lesions which stenosis is responsible for myocardial ischemia and consequently, whether the patient will be improved by revascularization of one or several stenoses. Non-invasive stress tests indicate with a high sensitivity that a myocardial region becomes ischemic, but often are not refined enough to discriminate which coronary stenosis can be held responsible for the perfusion abnormality. It has been shown many times that the morphologic aspects of a stenosis as found at coronary angiography are a poor predictor of the significance of a stenosis. (1-3) The need for functional assessment of coronary stenoses thus is evident. Nowadays fractional flow reserve (FFR) measurements most commonly are used in the catheterization laboratory. As was discussed in the **introduction**, dysfunction of the microcirculation and submaximal hyperemia influence coronary flow velocity reserve (CFVR) and FFR measurements, when assessing the hemodynamic significance of a coronary stenosis.

The combination of flow and pressure measurements allows a more complete assessment of the coronary circulation. With the opportunity to measure a pressure gradient and distal coronary pressure together with flow or flow velocity, the functional significance of stenoses can be studied more in detail and insight in the microcirculation can be gained. This was the subject of the present thesis. It is noteworthy that more than 30 years ago the initial approach to assess coronary stenoses in animals, used the combination of flow and pressure measurements. The lack of miniaturized sensors at that time prohibited the application of this approach in patients.

The feasibility to define the diastolic flow - pressure gradient (v-dp) relation in coronary stenoses in humans was assessed, as described in **chapter 2**. Measurements were performed in 11 normal arteries, 20 intermediate stenoses and 7 severe stenoses before and after percutaneous transluminal angioplasty (PCI) and coronary stenting. To define the v-dp relation the diastolic data of single cardiac cycles at baseline, maximal and intermediate hyperemia were analyzed. Significant differences were found between the three groups. After PCI, the v-dp relation was almost comparable to the group with normal coronary arteries. In **chapter 3**, the diagnostic performance of the v-dp relation to detect hemodynamic significant stenoses was compared to the CFVR and FFR. In 77 patients, 124 coronary vessels with a coronary stenosis were analyzed. All patients underwent prior to the intracoronary measurements non invasive stress testing. In this study, the diastolic data of all cardiac cycles from peak hyperemia to return of baseline condition (on average 20 to 30 cardiac cycles) were used to calculate the v-dp relation. The single instantaneous flow velocity value of the v-dp relation, yielding the highest diagnostic accuracy to detect a significant stenosis, was determined based on the results of the non invasive stress tests. The highest accuracy for all measurements was found at a flow velocity of 50 cm/sec; at this flow velocity the cut-off value to discriminate mild and significant stenoses was 22.4 mm Hg. This new index to assess the physiological severity of a coronary stenosis was called the dp_{v50} . Compared to FFR, the dp_{v50} yielded a higher sensitivity and a comparable specificity. The diagnostic accuracy of CFVR was lower compared to FFR and dp_{v50} . It was demonstrated that maximum hyperemia was not required to reliably assess the dp_{v50} . Characteristics of the v-dp relation were assessed in an in vitro model and are described in **chapter 4**. The v-dp relation of individual stenoses was compared in the presence or absence of a distal stenosis. It was found that in the

presence of a distal stenosis, the v-dp relation of the proximal stenosis is not affected. Furthermore, the v-dp relation of the consecutive stenoses was found to equal the sum of the v-dp relation of the individual stenoses. The diameter of the site where flow velocity was measured had a large effect on the v-dp relation of a given stenosis. To compare the v-dp relation of similar stenoses (minimal lumen diameters and length) but with different reference diameters, volume flow instead of flow velocity should be used. Finally, the presence of 1 or 2 wires in a stenosis significantly influenced the v-dp relation of a mild, intermediate or severe stenosis.

Future perspectives of the v-dp relation and dp_{v50} .

The major difference between the dp_{v50} and CFVR or FFR is that the dp_{v50} of a coronary stenosis can be assessed irrespective of the presence of a distal stenosis, microvascular dysfunction or submaximal hyperemia. Therefore this index is truly lesion specific. Although the value of the v-dp relation and dp_{v50} in the detection of significant stenoses is clear, a number of steps have to be taken before this index can be widely applied in catheterization laboratories in daily practice. In the present studies, the dp_{v50} always was measured using two wires. Nowadays a single wire (Combwire) is commercially available allowing for simultaneous pressure and flow velocity measurements. Since a second wire in a stenosis causes a considerable additional flow obstructing effect, the dp_{v50} cut-off value has to be re-established using the Combwire. Using this new cut-off value, a prospective study has to be done to assess the diagnostic accuracy of the dp_{v50} in comparison to FFR, as suggested by L Gould.(4). Furthermore, software has to be developed, allowing immediate and online calculation of the dp_{v50} . Similar to the DEFER study, a prospective study should be started to evaluate the safety of deferring a revascularization procedure, based on dp_{v50} results. (5)

Since the dp_{v50} is completely independent of the peripheral situation of the coronary artery, it would be interesting to study whether the dp_{v50} value of a stenosis can be predicted based on very precise morphological information, such as nowadays can be provided by intravascular ultrasound. This would require the availability of appropriate hydrodynamic equations. In the past, Young and Tsai have developed hydrodynamic laws that accurately predicted the hemodynamics of artificially induced stenoses in animals. (6-10) However when we applied these laws in our in vitro study, as described in chapter 4, a large discrepancy was found between the predicted and experimentally derived results; in all measurements the v-dp relation was much steeper than predicted. In contrast to the animal experiments, we studied stenoses with a sharp entrance and exit angle. This factor is not accounted for in the hydrodynamic equations we used. In our opinion, complex computational flow dynamics are needed to precisely predict the hemodynamics of real life coronary stenoses, which usually have a very irregular contour. As discussed earlier, v-dp relation or dp_{v50} value could be an appropriate measure to express the hemodynamic significance. If accurate computational flow dynamics could be successfully developed and validated, and if the morphology of a coronary stenosis could be described by an extremely precise non invasive imaging technique, it could become possible to assess the hemodynamic significance of coronary stenoses in a non-invasive way.

The study of the microcirculation is important. It has become increasingly clear that microvascular dysfunction is a frequent problem with many causes.(11) In patients with obstructive coronary artery disease, it is necessary to measure distal

coronary pressure to specifically assess MR without the confounding effect of an epicardial resistance. Therefore the availability of combined flow and pressure measurements provide the tools to study the microcirculation and microvascular resistance in patients.

In **chapter 5** two indices were studied to assess microvascular resistance (MR) in coronary arteries with a stenosis. Special attention was given to coronary arteries with a severe stenosis, where conflicting results on MR values have been reported. The first index used was the inverse slope of the distal coronary pressure - flow velocity relation, assessed in diastole and during maximum hyperemia (inv dpv slope). The second MR index was the ratio of mean distal coronary pressure and flow velocity, both averaged over one cardiac cycle, during maximal hyperemia (HMRI). Flow velocity and distal coronary pressure measurements of sufficient quality were acquired in 133 coronary arteries and were further analyzed. Several hemodynamic criteria were applied to separate mild and severe stenoses. No difference in inv dpv slope was found in coronary arteries with a severe stenosis, whereas HMRI was significantly higher in severe stenoses. The main physiological difference between the inv dpv slope and HMRI, is the fact that the former is least influenced by confounding hemodynamic factors, such as ventricular contraction, heart rate and aortic pressure. The fact that HMRI is pressure dependent and probably takes collateral flow not well into account also might explain the different results.

Evaluation of MR in infarct areas is particularly complex since these areas are composed of viable myocardium and scar tissue. Therefore, the amount of residual viable myocardium in an infarct area is smaller compared to a reference area. This influences the myocardial blood flow measurements required to determine the MR. In **chapter 6** the MR in viable myocardium after chronic infarction was compared to a reference area. $H_2^{15}O$ positron emission tomography (PET) was used to provide myocardial blood flow measurements. In infarct regions, $H_2^{15}O$ PET exclusively measures flow in viable myocardium, excluding flow in scar tissue. Furthermore PET provides flow data expressed per ml viable myocardium. In this manner the smaller amount of viable myocardium within an infarct region can be accounted for, when comparing flow values in infarct and reference areas. Distal coronary pressure was measured in the infarct related and reference artery. MR was defined as the ratio of mean distal pressure and flow, and was assessed at baseline and during hyperemia. Only PET flow data of true infarct segments (wall motion abnormalities or baseline perfusion defects at nuclear scintigraphy) were used. Measurements were performed in 27 patients. The average time between PET study and infarction was 3.3 ± 4.4 years. The MR in viable, chronically infarcted myocardium was not higher compared to the reference area during hyperemia. This finding was put into perspective. (12) An implication of this result was further assessed in **chapter 7**. In this study we analyzed whether FFR measurements were influenced by microvascular function in viable myocardium after chronic infarction. The same patient group studied in chapter 5 was used for this analysis. The methodology was identical to a previous study that validated the use of FFR measurements in patients without myocardial infarction. (13) The hypothesis tested was that if MR in the infarct related and reference area are equal, FFR values should be identical to relative flow reserve (RFR) measurements. If MR in the infarct area was increased compared to the reference area, FFR values would be higher compared to the corresponding RFR measurements. A secondary goal of this study was to define the FFR cut-off value based on the results of non-invasive stress tests. In order to apply the same methodology as the study of De Bruyne et al. the segmental PET flow data were clustered into 3 larger myocardial

regions, corresponding to the territory of the 3 coronary arteries. A good correlation between RFR and FFR was found; the linear regression line was close to the line of identity. Therefore MR in the viable myocardium and reference was found not to be different. The FFR cut-off value to detect hemodynamic stenoses was <0.79 which was similar to previous studies after infarction and is close to the established 0.75 value in patients without prior infarction.

Future perspectives to study the microcirculation.

Nowadays there is no perfect index to assess MR. The inv dpv slope probably is a good index. (14) Instead of using a pressure and a Doppler wire, the Combwire would be more appropriate to assess the inv dpv slope. When using MR indices based on the mean pressure and flow averaged over a cardiac cycle, the zero flow pressure should be accounted for in the pressure measurements. The zero flow pressure is very difficult to assess in humans. This problem could be circumvented by measuring blood flow and pressure at different levels of arterial pressure. But in this event, reflex activation of the autonomous system should be blocked. (15)

Studies could be undertaken to define MR reference values (normal - abnormal). to investigate more into detail the pathogenesis and pathophysiology of myocardial ischemia (e.g. in acute coronary syndromes, acute myocardial infarction, syndrome X, the metabolic syndrome,...) and to evaluate possible therapeutic strategies to treat these disorders.

To assess the microcirculation and MR, ideally one should be informed on the amount of blood flow per unit of myocardial volume. This would allow for measurement and comparison of MR values in comparable volumes of myocardial tissue. Collateral flow fully would be included in the flow data. In our opinion, it would be most appropriate to use several blood flow measurements in the diastolic phase of a cardiac cycle (with concomitant distal pressure measurements) during hyperemia. These serial diastolic flow and pressure measurements could be used to determine a (distal) pressure - volume flow relation. However, nowadays there is no technique that can give absolute myocardial blood flow data with a high temporal and spatial resolution.

REFERENCES

1. **Brueren BR, ten Berg JM, Suttorp MJ, Bal ET, Ernst JM, Mast EG and Plokker HW.** How good are experienced cardiologists at predicting the hemodynamic severity of coronary stenoses when taking fractional flow reserve as the gold standard. *Int J Cardiovasc Imaging* 2002 Apr 73-76, 1918.
2. **Topol EJ and Nissen SE.** Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. *Circulation* 1995 Oct 15 2333-2342, 1992.
3. **White CW, Wright CB, Doty DB, Hiratza LF, Eastham CL, Harrison DG and Marcus ML.** Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? *N Engl J Med* 1984 Mar 29 819-824, 310.
4. **Gould KL.** Physiological severity of coronary artery stenosis. *Am J Physiol Heart Circ Physiol* 291: H2583-H2585, 2006.
5. **Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, Bar F, Hoorntje J, Koolen J, Wijns W and de Bruyne B.** Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol* 2007 May 29 2105-2111, 1949.
6. **de Jong JP, Westerhof N and Elzinga G.** How to quantify an arterial stenosis: a study on the femoral arteries of dog and man. *Cardiovasc Res* 20: 134-144, 1986.
7. **Young DF and Tsai FY.** Flow characteristics in models of arterial stenoses. I. Steady flow. *J Biomech* 6: 395-410, 1973.
8. **Young DF, Cholvin NR and Roth AC.** Pressure drop across artificially induced stenoses in the femoral arteries of dogs. *Circ Res* 36: 735-743, 1975.
9. **Young DF, Cholvin NR, Kirkeeide RL and Roth AC.** Hemodynamics of arterial stenoses at elevated flow rates. *Circ Res* 41: 99-107, 1977.
10. **Gould KL, Kelley KO and Bolson EL.** Experimental validation of quantitative coronary arteriography for determining pressure-flow characteristics of coronary stenosis. *Circulation* 66: 930-937, 1982.
11. **Camici PG and Crea F.** Coronary microvascular dysfunction. *N Engl J Med* 356: 830-840, 2007.
12. **Pijls NH.** Fractional flow reserve after previous myocardial infarction. *Eur Heart J* 2007 28: 2301-2302, 2007.
13. **de Bruyne B, Baudhuin T, Melin JA, Pijls NH, Sys SU, Bol A, Paulus WJ, Heyndrickx GR and Wijns W.** Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. *Circulation* 89: 1013-1022, 1994.
14. **Klocke FJ, Mates RE, Canty JM, Jr. and Ellis AK.** Coronary pressure-flow relationships. Controversial issues and probable implications. *Circ Res* 56: 310-323, 1985.
15. **L'Abbate A, Sambuceti G, Haunso S and Schneider-Eicke J.** Methods for evaluating coronary microvasculature in humans. *Eur Heart J* 20: 1300-1313, 1999.