Characteristics of the flow velocity-pressure gradient relation in the assessment of stenoses: an in vitro study

K.M.J. Marques, N. Westerhof

Objectives. The flow velocity-pressure gradient (v-dp) relation is clinically used to assess coronary stenoses. This in vitro study aimed to investigate the ability to determine the impact of each individual stenosis in the setting of two consecutive stenoses, the effect of variable stenosis reference diameters and the impact of one or two wires in a stenosis, on the v-dp relation.

Methods. The model consisted of a reservoir and different sized tubes and stenoses. Pressure gradient and flow velocity were assessed with a pressure and a Doppler wire. By plotting flow velocity and pressure gradient on an X-Y plot, the v-dp relation was determined.

Results. The v-dp relation of a proximal stenosis was not influenced by a distal stenosis. The diameter of the segment where flow velocity was measured influenced the v-dp relation. This could be corrected by substituting flow velocity with volume flow. The presence of one or two wires in a stenosis made the v-dp relation substantially steeper.

Conclusions. The v-dp relation can be used to determine the significance of each individual stenosis in arteries with consecutive stenoses, provided that the distance between the stenoses is large enough. The diameter of the segment where flow velocity is measured and the presence of one or two wires substantially affect the v-dp relation. (*Neth Heart J* 2008;16:156-62.)

Keywords: physiology, coronary blood flow, haemodynamics

The physiological assessment of coronary stenoses is clinically important. In the catheterisation laboratory, most commonly the fractional flow reserve (FFR) and coronary flow velocity reserve (CFVR) are determined, using a pressure wire or a Doppler wire, respectively.^{1,2} The combined measurement of coronary pressure and flow velocity determines the flow impediment caused by a coronary stenosis, independent of the state of microcirculation. Both the hyperaemic stenosis resistance (HSR) and dp_{v50} , which is derived from the diastolic flow velocity-pressure gradient (v-dp) relation, have been found to determine the haemodynamic significance of a coronary stenosis with a high accuracy.³⁻⁶

Patients frequently have multiple stenoses in the same coronary artery. Compared with a single stenosis, multiple consecutive stenoses result in a greater reduction in maximal flow.⁷⁻⁹ Physiological assessment of the severity of each individual stenosis, using FFR or CFVR, is hampered by the fluid dynamic interaction between the stenoses. In an in vitro and a dog model it has been shown that the stenosis resistance of two consecutive stenoses equals the sum of each individual stenosis resistance, provided the distance between the stenoses is large enough.^{10,11} The diameter of a coronary artery distal to a stenosis may be pathologically wide or narrow (poststenotic dilatation or diffuse arteriosclerosis). As a consequence, flow velocity measured in such a segment will be lower or higher. It is not known how this affects the v-dp relation. In patients, assessment of the v-dp relation has been done with two wires in a coronary stenosis, resulting in an additional flow impediment.⁵ It is unknown to what extent the presence of one or two sensor wires affects the v-dp relation of a stenosis.

The purpose of the present study was to investigate some characteristics of the v-dp relation using a pressure and Doppler flow wire that are routinely used in clinical practice. More specifically, the following v-dp relation characteristics were investigated: A) the ability of the

K.M.J. Marques

Department of Cardiology, and Institute for Cardiovascular Research (ICaR-VU), VU University Medical Center, Amsterdam, the Netherlands

N. Westerhof

Department of Pulmonary Diseases and Physiology, and Institute for Cardiovascular Research (ICaR-VU), VU University Medical Center, Amsterdam, the Netherlands

Correspondence to: K.M.J. Marques
Department of Cardiology, VU University Medical Center,
PO Box 7057, 1007 MB Amsterdam, the Netherlands
E-mail: km.marques@vumc.nl

v-dp relation to determine the haemodynamic impact of each individual stenosis in the setting of two consecutive stenoses, B) the effect on the v-dp relation of variable reference diameters of the same stenosis and C) the effect of one or two wires in a stenosis. We used an in vitro model to study these effects on the v-dp relation.

Material and Methods

The in vitro model

The model (figure 1) consisted of an open Perspex (reservoir) tube with a height of 160 cm and an inner diameter of 3 cm. An exit was made 2 cm above the bottom of the tube allowing, by virtue of a Y-connector, for the measurement of reservoir pressure and introduction of sensor wires (a). At the same level at the other site of the reservoir, a horizontal Perspex tube (b) was connected. At this point, elastic non-compliant tubes (c) with different inner diameters (5 or 7 mm) could be connected. A proximal stenosis (d) was connected at 25 cm from the reservoir. If a single stenosis was to be evaluated, 6 cm of tube (e) was connected distal to the stenosis. In case of two consecutive stenoses, 6 cm tube was interposed (e) and a 6 cm piece of tube (e) was connected to the distal stenosis (f). After placing a clamp on the elastic tube, the reservoir was

filled. Before removing the clamp, recording of flow velocity and pressure data (see below) was started. The fluid, a 40% aqueous glycerol solution, was collected and reused. Cornstarch was added to allow for flow velocity measurements with the Doppler wire. The viscosity of this solution was determined with an Ostwald viscosimeter. At 20 °C, a viscosity of 0.046 poise was found (blood = 0.035 poise).

Four different non-compliant Perspex stenoses were studied. Three had a reference (inner) diameter of 5 mm, a stenosis length of 20 mm and a minimal lumen diameter of 1.49 mm (stenosis A), 2.5 mm (stenosis B) and 3.52 mm (stenosis C), resulting in a 70, 50 and 30% diameter stenosis, respectively. The fourth stenosis (stenosis D) had a reference diameter of 7 mm at one side and 5 mm at the other site, a stenosis length of 20 mm and a minimal lumen diameter of 2.5 mm.

Flow velocity and pressure measurements

The pressure in the reservoir at the level of the stenosis was measured with a fluid-filled pressure system. Flow velocity (v) was measured with a Doppler FloWire (Volcano Corporation, Rancho Cordova, CA, USA) and the Jometrics Flomap. The FloWire has a 15-MHz piezoelectric ultrasound transducer integrated onto its tip. Doppler flow velocity is measured approximately

Figure 1. Schematic representation of the model (not in scale). a=the Y connector to introduce wires and to measure reservoir pressure, b=horizontal Perspex tube, c=elastic non-compliant tube, d=proximal stenosis, e=6 cm elastic tube, f=distal stenosis. * indicates site of flow velocity measurement and ↑ (1-3) locations of pressure measurement with pressure wire.

5 mm from the tip. The ultrasound beam, directed forward at a divergent angle of 28°, samples along a portion of the flow profile. Velocity of flow is calculated from the Doppler frequency shift equation based on changes in frequency between transmitted and returning signals, and the data are processed by on-line fast Fourier transformation. To record peak instantaneous flow velocities, the tip of the wire was bent and the Doppler wire was rotated until an optimal signal-noise ratio was obtained. To determine the pressure gradient, pressure was measured proximal and distal to a stenosis with the BrightWire II (Volcano Corporation, Rancho Cordova, CA, USA) and the ComboMap (Volcano Therapeutics, Rancho Cordova, CA, USA). Both the Doppler and pressure wires have a diameter of 0.35 mm (0.014 inch). Flow velocity recordings were always performed with the wire positioned 5 cm proximal to the (first) stenosis (asterisk in figure 1). To determine the pressure gradient (dp), pressure measurements were always performed 2 cm proximal to the first or second stenosis (first and second vertical arrow in figure 1) and 4 cm distal to the first or second (second and third vertical arrow) stenosis.

Different settings

The v-dp relation of the single stenoses A, B and C was determined in three settings: without wire, with one and with two wires in the stenosis. In the setting without wire in the stenosis, distal pressure was measured by retrograde introduction of the pressure wire with the sensor positioned 4 cm distal to the stenosis. In the setting of one wire in the stenosis, proximal pressure was recorded with one idle wire in the stenosis. In the setting of two wires in the stenosis, proximal pressure was recorded with two idle wires and distal pressure with one idle wire in the stenosis.

To study the v-dp relation of the proximal stenosis in the presence of a distal stenosis, the setting of one wire in a stenosis was used. Stenoses A, B or C were combined with one of the remaining two (six possible combinations). In each of these six combinations, first the v-dp relation of the proximal stenosis alone was assessed (using the pressure recordings at location 1 and 2). Afterwards, the v-dp relation of the stenoses in series was determined (using pressure recordings at location 1 and 3).

The effect of variable reference diameters of the same stenosis was studied using stenoses B and D. Both these stenoses had a minimal internal diameter of 2.5 mm and a length of 20 mm. Stenosis B had a proximal and distal reference diameter of 5 mm; stenosis D had a reference diameter of 7 mm at one site and 5 mm at another site. Using stenosis D, first flow velocity measurements were performed in the 5 mm elastic tube (item c in figure 1); the distal tube (item d) had a diameter of 7 mm. Then stenosis D was reversed, resulting in a 7 mm proximal segment (location of flow velocity measurement) which was connected to a 7 mm wide elastic tube (item c) at the

proximal site and a 5 mm wide tube to the distal segment.

Calculation of the v-dp relation

Reservoir pressure, pressure wire data and flow velocity measurements were sampled at 100 Hertz and recorded on a computer. Before starting a measurement, it was verified that pressure in the reservoir was equal to pressure measured with the pressure wire. All measurements were performed twice to assess variability.

To determine the v-dp relation of a given setting, three different measurements had to be obtained: 1) simultaneous reservoir pressure and flow velocity measurement, 2) simultaneous reservoir pressure and proximal pressure measurement and 3) simultaneous reservoir pressure and distal pressure measurement. The pressure gradient was the difference between proximal (location 1) and distal pressure (location 2 or 3) at the same reservoir pressure. Since proximal and distal pressure were not measured simultaneously, they were first plotted in relation to reservoir pressure. The flow velocity data were also related to reservoir pressure. For each reservoir pressure value, thus, the corresponding flow velocity value and proximal and distal pressure data were known. Thus, the instantaneous pressure gradient could be related to the instantaneous flow velocity. These data were plotted with flow velocity on the X-axis and pressure gradient on the Y-axis. The v-dp relation was fitted using a second degree equation: $\Delta p = av + bv^2$.¹² The v-dp relation of stenoses A, B and C with one wire in the stenosis is displayed in figure 2.

The mathematical sum of the v-dp relation of two single stenoses was compared with the v-dp relation of both stenoses in series. To obtain the mathematical sum of two (single) v-dp relations, for each (common)

Figure 2. v-dp relation of stenoses A to C with one wire in stenosis. The mathematical equation is displayed.

Figures 3A to C. v-dp relation of single stenosis A, B or C (full line) and stenosis A, B or C being proximal to one of the other two stenoses (dashed lines). Different scales are used.

flow velocity value the corresponding pressure gradients were summed.

For stenoses B and D, not only the v-dp relation but also the volume flow-pressure gradient relation was determined. In straight tubes of uniform diameter, the velocity profile over the cross-section is a parabola. It has been shown that the peak instantaneous flow velocity measured with a Doppler wire is exactly twice the mean velocity.¹³ To calculate volume flow, peak flow velocity was multiplied with 0.5 to get mean flow velocity and mean flow velocity was multiplied with the cross-sectional area of the reference segment.

Statistical analysis

To quantify the difference between two v-dp relations, for each flow velocity value (within the common flow velocity range of the two v-dp relations) the ratio of the pressure gradient difference and the mean pressure gradient was determined. The average of this ratio was calculated.

Results

A variation of 5 and 1% was found for duplicate flow velocity and pressure measurements, respectively.

In figure 3, the v-dp relation of single stenosis A, B or C (full line) was compared with the v-dp relation of the same stenosis in the presence of a distal stenosis (dashed line). For the sake of clarity, different scales on the X- and Y-axes were used in figures 3A to C. It can be appreciated that the dashed regression lines hardly differ from the full lines. The mean difference between the full and dashed lines ranged from 0 to 6%. The mathematical sum of the v-dp relation of single stenoses (short dashes) was compared with the (measured) v-dp relation of the same stenoses in series (long dashes), as is illustrated in figure 4 for stenoses B and C. The

Figures 4. v-dp relation of single stenoses B and C with one wire (solid line); v-dp relation of stenoses B and C in series (long dashes); mathematical sum of the v-dp relation of single stenoses B and C (short dashes)

combination of stenoses A and B, and A and C was also assessed. The mean difference between the serial and summed v-dp relations for these three combinations ranged from 1 to 5%.

The effect on the v-dp relation of variable reference diameters of the same stenosis is demonstrated in figure 5A. When flow velocity was measured in the 5 mm reference segment of stenoses B and D (full line and short dashes), the v-dp relations were close together. However, when flow velocity was measured in the 7 mm wide reference segment of (reversed) stenosis D

(long dashes), the v-dp relation became steeper. When flow velocity was substituted by volume flow, the volume flow-dp relations for the three different situations were nearly identical (figure 5B). The mean difference between the volume flow-dp relation of stenosis B and D was 10%, and between B and reversed D was 5%.

The effect on the v-dp relation of one or two wires in a stenosis is shown in figures 6A to C. After introduction of one wire in a stenosis, the v-dp relation was 55, 32 and 30% steeper in stenoses A, B and C, respectively. Compared with the situation without wire, the presence of two wires made a difference of 137, 83 and 71% for stenoses A, B and C, respectively.

Discussion

The present in vitro study showed that for consecutive stenoses, the v-dp relation of the proximal stenosis is not influenced by a distal stenosis, as illustrated in figure 3. This finding was further confirmed by the fact that the v-dp relation of two consecutive stenoses equalled the mathematical sum of the v-dp relations of each individual stenosis. This implicates that for consecutive stenoses the v-dp relation of a distal stenosis can be calculated as the difference between the v-dp relation of the serial stenoses and proximal stenosis. These findings are in agreement with a study in a dog model. The resistances of coronary stenoses in series, measured with an electromagnetic flow meter and a pressure transducer, were shown to be additive.^{10,11} This is in contrast to FFR measurements in serial stenoses. The interaction between the two stenoses is such that FFR of each lesion separately can not be calculated by the equation for isolated stenoses. For serial stenoses a more complex equation, which takes into account the pressure between the two stenoses and the wedge pressure, can be used to determine the true FFR of each lesion separately.^{14,15}

Normally the diameter of coronary arteries gradually declines in proportion to the myocardial mass to be perfused. Therefore, mean coronary flow velocity is the same throughout the epicardial coronary system and thus the site where flow velocity is measured has no impact on the v-dp relation.¹⁶ Some patients have aneurysmatic coronary arteries or a poststenotic dilatation. When flow was measured in a wide segment, flow velocities were lower and the v-dp relation became steeper, as demonstrated in figure 5. When flow velocity was substituted by volume flow, however, the vessel diameter where flow velocity was measured no longer mattered. The diameter of the site where distal pressure was measured also had a small effect on the v-dp relation (difference between full line and line with small dashes in figures 5A and 5B).

The presence of one or two wires in a stenosis had a substantial effect on the v-dp relation. This effect was not only marked in a severe stenosis (A) but also in intermediate and mild stenoses (B and C). According

Figures 5. A) v-dp relation of single stenoses B and D (identical minimal lumen diameters and length but variable proximal and distal reference diameters); v-dp relation of stenosis B (full line); v-dp relation of stenosis D with flow velocity measured in 5 mm reference segment (long dashes); v-dp relation of (reversed) stenosis D with flow velocity measured in 7 mm reference segment (short dashes). B) volume flow-pressure gradient relation for the same stenoses.

Figures 6A to C. v - dp relation of single stenoses A, B or C without (full line), with one wire (short dashes) and with two wires (long dashes) in the stenosis.

to fluid dynamic principles, an inverse relation exists between the degree of flow impediment due to the presence of one or two wires (cross-sectional area 0.12 mm²), and the minimal luminal diameter of the vessel. This implies that in severe stenoses, the degree of flow impediment is larger than in intermediate stenoses. As has been previously reported, we also found that the percentage overestimation for the same stenosis was little influenced by the flow velocity rate.¹⁷ The clinical implication of an increased coronary resistance due to the presence of one or two wires is only relevant for intermediate stenoses. Physiological measurements in severe stenoses (stenosis A) are rarely needed for decision making; haemodynamic indices (with one or two wires) will always be found to be very pathological. In mild stenoses (stenosis C), the presence of one or two wires only induced a minor absolute increase in pressure gradient for a given flow velocity. For example, the pressure gradient at a flow velocity of 50 cm/sec (dp_{v50}) in stenosis C increased 1 mmHg with one wire and 2 mmHg with the presence of two wires. The dp_{v50} remained well below the established cut-off value (22.4 mmHg) to detect haemodynamic stenoses.⁶ For intermediate stenoses (stenosis B), the dp_{v50} with one wire was below the cut-off value; the introduction of a second wire, however, resulted in a pathological dp_{v50} value. These findings are in agreement with a clinical study in intermediate stenoses that showed that the presence of two wires is associated with overestimation of the haemodynamic effect of a coronary stenosis severity and had a negative influence on decision making.¹⁸

With this in vitro model the human coronary situation in diastole was partially simulated. Measurements were performed with sensor wires routinely used in patients. A 40% aqueous glycerol solution was used, with a viscosity similar to blood. Due to the addition of cornstarch, however, viscosity was found to rise by 31%. Viscosity has a linear relation with pressure gradient when flow is laminar (Poiseuille's law). Furthermore, viscosity is inversely related to the Reynolds number. Laminar flow occurs at low Reynolds numbers. To correct the v - dp relations of the present study to a condition with the viscosity of blood (0.035 poise), the coefficient in the equation $p = av + bv^2$, should be multiplied by a factor 0.76 (0.035/0.046). The higher than physiological viscosity, however, does not have any impact on the conclusions of the present study. Since coronary flow in mid diastole is characterised by a gradually declining flow velocity without acceleration or deceleration, we simulated diastolic coronary flow in the model by the emptying of a reservoir. The distal pressure in the model was the atmospheric pressure. This feature has no impact on the findings of the present study since the v - dp relation is independent of distal resistance. In contrast to clinical practice, in the present study flow velocity was always measured proximal to the first stenosis. Since there are no side branches in the model, this has no consequences.

Limitations

When the distance between two lesions is greater than six times the vessel diameter, they generally behave independently. However, when the distance between two stenoses is very short or a proximal stenosis is closely followed by a very severe distal stenosis, the pressure drop over the first stenosis is smaller. In this setting (all) indices based on pressure gradients, including the v-dp relation, will underestimate the haemodynamic significance of the proximal stenosis.¹⁰ In the present model, the distance between the two stenoses was 6 cm (12 times vessel diameter). The interaction between stenoses with a shorter distance was not studied.

Conclusions

In the setting of consecutive stenoses, the v-dp relation can be used to determine the haemodynamic impact of each individual stenosis, provided the distance between the stenoses is large enough. If the diameter of the site where flow velocity is measured is abnormally wide, it is better to use volume flow instead of flow velocity to assess the haemodynamic impact of a stenosis. The presence of one or two wires in a stenosis substantially affects the v-dp relation. ■

References

- Pijls NH, Van Gelder B, Van Der Voort PH, Peels K, Bracke FA, Bonnier HJ, et al. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation* 1995;**92**:3183-93.
- Bach RG, Kern MJ. Practical coronary physiology. Clinical application of the Doppler flow velocity guide wire. *Cardiol Clin* 1997;**15**:77-99.
- Meuwissen M, Siebes M, Chamuleau SA, Eck-Smit BL, Koch KT, de Winter RJ, et al. Hyperemic stenosis resistance index for evaluation of functional coronary lesion severity. *Circulation* 2002;**106**:441-6.
- Siebes M, Verhoeff BJ, Meuwissen M, de Winter RJ, Spaan JA, Piek JJ. Single-wire pressure and flow velocity measurement to quantify coronary stenosis hemodynamics and effects of percutaneous interventions. *Circulation* 2004;**109**:756-62.
- Marques KM, Spruijt HJ, Boer C, Westerhof N, Visser CA, Visser FC. The diastolic flow-pressure gradient relation in coronary stenoses in humans. *J Am Coll Cardiol* 2002;**39**:1630-6.
- Marques KM, van Eenige MJ, Spruijt HJ, Westerhof N, Twisk J, Visser CA, et al. The diastolic flow velocity-pressure gradient relation and dpv50 to assess the hemodynamic significance of coronary stenoses. *Am J Physiol Heart Circ Physiol* 2006;**291**:H2630-5.
- Sabbah HN, Stein PD. Hemodynamics of multiple versus single 50 percent coronary arterial stenoses. *Am J Cardiol* 1982;**50**:276-80.
- Feldman RL, Nichols WW, Pepine CJ, Conti CR. Hemodynamic effects of long and multiple coronary arterial narrowings. *Chest* 1978;**74**:280-5.
- Karayannacos PE, Talukder N, Nerem RM, Roshon S, Vasko JS. The role of multiple noncritical arterial stenoses in the pathogenesis of ischemia. *J Thorac Cardiovasc Surg* 1977;**73**:458-69.
- Gould KL, Lipscomb K. Effects of coronary stenoses on coronary flow reserve and resistance. *Am J Cardiol* 1974;**34**:48-55.
- Dodds SR, Phillips PS. The haemodynamics of multiple sequential stenoses and the criteria for a critical stenosis. *Eur J Vasc Endovasc Surg* 2003;**26**:348-53.
- Young DF, Tsai FY. Flow characteristics in models of arterial stenoses. I. Steady flow. *J Biomech* 1973;**6**:395-410.
- Doucette JW, Corl PD, Payne HM, Flynn AE, Goto M, Nassi M, et al. Validation of a Doppler guide wire for intravascular measurement of coronary artery flow velocity. *Circulation* 1992;**85**:1899-911.
- de Bruyne B, Pijls NH, Heyndrickx GR, Hodeige D, Kirkeeide R, Gould KL. Pressure-derived fractional flow reserve to assess serial epicardial stenoses: theoretical basis and animal validation. *Circulation* 2000;**101**:1840-7.
- Pijls NH, de Bruyne B, Bech GJ, Liestro F, Heyndrickx GR, Bonnier HJ, et al. Coronary pressure measurement to assess the hemodynamic significance of serial stenoses within one coronary artery: validation in humans. *Circulation* 2000;**102**:2371-7.
- Anderson HV, Stokes MJ, Leon M, Abu-Halawa SA, Stuart Y, Kirkeeide RL. Coronary artery flow velocity is related to lumen area and regional left ventricular mass [In Process Citation]. *Circulation* 2000;**102**:48-54.
- de Bruyne B, Pijls NH, Paulus WJ, Vantrimpont PJ, Sys SU, Heyndrickx GR. Transstenotic coronary pressure gradient measurement in humans: in vitro and in vivo evaluation of a new pressure monitoring angioplasty guide wire. *J Am Coll Cardiol* 1993;**22**:119-26.
- Verberne HJ, Meuwissen M, Chamuleau SA, Verhoeff BJ, Eck-Smit BL, Spaan JA, et al. Effect of simultaneous intracoronary guide wires on the predictive accuracy of functional parameters of coronary lesion severity. *Am J Physiol Heart Circ Physiol* 2007;**292**:H2349-55.