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Reply to the letter to the editor by Saito regarding the article "In vivo validation of mathematically derived fractional flow reserve for assessing haemodynamics of coronary tandem lesions"

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This paper also includes supplementary data published online at: http://www.pcronline.com/eurointervention/132nd_issue/339

We appreciate the interest in our article[1]. The author (N. Saito) raised the issue of fundamental errors in the primary assumption for the mathematical model of FFR post-stenting and suggested that the application of the prediction model in Yamamoto et al[2] would improve the outcomes of FFR prediction.

The flow rate (Q) in our derivation is defined as the coronary flow (not as the perfusion flow), which determines the translesional pressure gradient[3]. It is well established that the coronary flow is proportional to the difference between the distal pressure and the wedge pressure[4]. This is also the first equation for the model derivation of De Bruyne et al[5], which was considered as the "conventional model" for the comparison in our publication. Because the same assumptions were made for the derivation, the prediction equations of our model are inherently equivalent to those of De Bruyne et al[2]. We believe our mathematical derivation is founded on the well-established knowledge of coronary physiology.

In the validation of our model, the predicted FFR values were situated within the band of true FFR±0.03 or slightly overestimated. When w=1 is used as suggested, instead of w=1.33 in our derivation, the denominator in the equation becomes larger and the predicted FFR values are further overestimated.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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1. Kweon J, Kim YH, Yang DH, Lee JG, Roh JH, Mintz GS, Lee SW, Park SW. In vivo validation of mathematically derived fractional flow reserve for assessing hemodynamics of coronary tandem lesions. *EuroIntervention.* 2016;12:e1375-84.

2. Yamamoto E, Saito N, Matsuo H, Kawase Y, Watanabe S, Bao B, Watanabe H, Higami H, Nakatsuma K, Kimura T. Prediction of the true fractional flow reserve of left main coronary artery stenosis with concomitant downstream stenoses: in vitro and in vivo experiments. *EuroIntervention.* 2016;11:e1249-56.

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5. 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.

Supplementary data

Both of the letters to the Editor disputing the paper, "In vivo validation of mathematically derived fractional flow reserve for assessing haemodynamics of coronary tandem lesions"[1], together with all further correspondence can be found online in the **Supplementary data**.

The supplementary data are published online at: http://www.pcronline.com/eurointervention/132nd_issue/339

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Supplementary data

LETTER TO THE EDITOR BY SAITO

Letter regarding the article: “In vivo validation of mathematically derived fractional flow reserve for assessing haemodynamics of coronary tandem lesions”

Reconsideration of a mathematical model for post stenting fractional flow reserve in a tandem lesion with a side branch

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I read with interest the paper by Kweon and colleagues [1] in which they proposed a prediction model for post-stenting fractional flow reserve (FFR) in a tandem lesion with a side branch. The authors derived the following two equations that predicted the FFR after treatment of distal (Equation 1) or proximal stenosis (Equation 2):

$$\mathrm{FFR}'_{d,\mathrm{pred}} = \mathrm{FFR}_p - \frac{\Delta\mathrm{FFR}_p}{1 - wk\Delta\mathrm{FFR}_d} = \mathrm{FFR}_p - \frac{\Delta\mathrm{FFR}_p}{1 - 1.33 \times k\Delta\mathrm{FFR}_d} \quad (1)$$

$$\mathrm{FFR}'_{d,\mathrm{pred}} = \mathrm{FFR}_p - \frac{\Delta\mathrm{FFR}_d}{1 - w\Delta\mathrm{FFR}_p} = FFR_p - \frac{\Delta\mathrm{FFR}_d}{1 - 1.33\Delta\mathrm{FFR}_p}, \quad (2)$$

where $w=P_a/(P_a-P_w)=1.33$ and $k=Q_1/Q_0$. Their efforts are praiseworthy; however, they committed a serious error in their calculation. The authors calculated the hyperaemic coronary flow to each branch by using the P=QR equation. The problem is that the authors always calculated perfusion pressure as the difference between the distal coronary pressure and the wedge pressure (e.g., P_d-P_w). However, the perfusion driving pressure should be the difference between the distal coronary pressure and the central venous pressure (e.g., P_d-P_v), and P_v is usually considered zero when calculating the FFR [2]. The authors committed the same error in all their calculations. It seems that the bifurcation model described in the present study did not include the collateral supply. Thus, $w=P_a/(P_a-P_v)=1$ is correct and should be applied in Equations 1 and 2.

$$FFR'_{d,\mathrm{pred}} = \mathrm{FFR}_p - \frac{\Delta\mathrm{FFR}_p}{1 - wk\Delta\mathrm{FFR}_d} = \mathrm{FFR}_p - \frac{\Delta\mathrm{FFR}_p}{1 - k\Delta\mathrm{FFR}_d} \quad (1')$$

$$\mathrm{FFR}'_{d,\mathrm{pred}} = \mathrm{FFR}_p - \frac{\Delta\mathrm{FFR}_d}{1 - w\Delta\mathrm{FFR}_p} = \mathrm{FFR}_p - \frac{\Delta\mathrm{FFR}_d}{1 - \Delta\mathrm{FFR}_p} \quad (2')$$

Equations 1′ and 2′ are the correct equations.

We have already described the same equation in our previous study that analysed the true FFR of the left main coronary lesion with a downstream stenosis [3]. The equation is as follows:

$$\mathrm{FFR}_{\mathrm{pred}-m} = \frac{n\mathrm{FFR}_1 + \mathrm{FFR}_m}{1 + n(1 - [\mathrm{FFR}_m - \mathrm{FFR}_1])}, \quad (3)$$

where n is defined as the ratio of the microcirculatory resistance of the side branch to that of the main branch, and $\mathrm{FFR}_m=P_m/P_a$, and $\mathrm{FFR}_1=P_d/P_a$. The relationship of $n=k/(1-k)$, $\Delta\mathrm{FFR}_p=1-\mathrm{FFR}_m$, and $\Delta\mathrm{FFR}_d=\mathrm{FFR}_m-\mathrm{FFR}_1$ is true; thus, Equation 3 can be transformed to Equation 1′ as follows:

$$\mathrm{FFR}_{\mathrm{pred}-m} = \frac{\frac{k}{1-k}(1 - \Delta\mathrm{FFR}_p - \Delta\mathrm{FFR}_d) + (1 - \Delta\mathrm{FFR}_p)}{1 + \frac{k}{1-k}(1 - \Delta\mathrm{FFR}_d)}$$

$$= 1 - \frac{\Delta\mathrm{FFR}_p}{1 - k\Delta\mathrm{FFR}_d}$$

$$= \mathrm{FFR}_p - \frac{\Delta\mathrm{FFR}_p}{1 - k\Delta\mathrm{FFR}_d}$$

Note that FFR_p is always equal to 1.

I recommend that the authors reanalyse their data by using Equations 1′ and 2′, which will certainly bring more correct results and improve the quality of the paper.

Conflict of interest statement

The author has no conflicts of interest to declare.

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1. Kweon J, Kim YH, Yang DH, Lee JG, Roh JH, Mintz GS, Lee SW, Park SW. In vivo validation of mathematically derived fractional flow reserve for assessing haemodynamics of coronary tandem lesions. EuroIntervention. 2016;12:e1375-e1384.
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REPLY TO THE LETTER TO THE EDITOR FROM SAITO ET AL

Reply to the letter to the editor by Saito regarding the article "In vivo validation of mathematically derived fractional flow reserve for assessing haemodynamics of coronary tandem lesions"

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We appreciate the interest in our article [1]. The author (N. Saito) raised the issue of fundamental errors in the primary assumption for the mathematical model of FFR post-stenting and suggested that the application of the prediction model in Yamamoto et al [2] would improve the outcomes of FFR prediction.

The flow rate (Q) in our derivation is defined as the coronary flow (not as the perfusion flow), which determines the translesional pressure gradient [3]. It is well established that the coronary flow is proportional to the difference between the distal pressure and the wedge pressure [4]. This is also the first equation for the model derivation of De Bruyne et al [5], which was considered as the "conventional model" for the comparison in our publication. Because the same assumptions were made for the derivation, the prediction equations of our model are inherently equivalent to those of De Bruyne et al [5]. We believe our mathematical derivation is founded on the well-established knowledge of coronary physiology.

In the validation of our model, the predicted FFR values were situated within the band of true FFR±0.03 or slightly overestimated. When w=1 is used as suggested, instead of w=1.33 in our derivation, the denominator in the equation becomes larger and the predicted FFR values are further overestimated.

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1ST RESPONSE FROM SAITO TO THE ORIGINAL AUTHORS

Response to the letter by Kweon et al regarding my letter to them:

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Kweon et al claimed that coronary flow is proportional to the difference between the distal pressure and the wedge pressure in their response letter. This is completely wrong. This misunderstanding probably comes from the misinterpretation of the fractional coronary flow reserve (FFR_{cor}) expressed in the following equation [1].

$$FFR_{cor} = \frac{coronary\ blood\ flow\ in\ the\ presence\ of\ coronary\ stenosis\ at\ maximal\ hyperemia}{normal\ coronary\ blood\ flow\ at\ maximal\ hypermia} = \frac{P_d - P_w}{P_a - P_w} \quad (A)$$

Note that all abbreviations and terminology are the same as in the original paper by Pijls et al [1]. At a glance, the above Equation A suggests that coronary flow is proportional to the difference between the distal pressure and the wedge pressure, but this is not true. Kweon et al will know why they made a misinterpretation after understanding how Equation A is derived.

$$FFR_{cor} = \frac{Q_s}{Q_s^N} = \frac{\frac{P_a - P_d}{R_s}}{\frac{P_a - P_v}{R}} \quad (1)$$

Here, $Q=Q_s+Q_c$, and $Q_s=Q-Q_c$ and $Q=(P_d-P_v)/R$ and $Q_c=(P_a-P_d)/R_c$, substituting these equations into Equation 1 gives,

$$FFR_{cor} = \frac{Q_s}{Q_s^N} = \frac{Q - Q_c}{Q^N} == \frac{\frac{P_d - P_v}{R} - \frac{P_a - P_d}{R_c}}{\frac{P_a - P_v}{R}} \quad (1')$$

The relationship between R and R_c is described as follows,

$$\frac{P_w - P_v}{R} = \frac{P_a - P_w}{R_c}$$

$$R_c = \frac{P_a - P_w}{P_w - P_v} \cdot R \quad (2)$$

Substituting Equation 2 into Equation 1' gives Equation A as follows,

$$FFR_{cor} = \frac{\frac{P_d - P_v}{R} - \frac{P_a - P_d}{\frac{P_a - P_w}{P_w - P_v} \cdot R}}{\frac{P_a - P_v}{R}} = \frac{P_d - P_w}{P_a - P_w}$$

In this form, it seems that the coronary flow is proportional to the difference between the distal pressure and the wedge pressure (P_d-P_w). However, going back to Equation 1, Q_s^N is proportional to the pressure difference between the aortic pressure and the venous pressure

(P_a-P_v), and also Q_s is proportional to the difference between proximal pressure and the distal coronary pressure (P_d-P_v): the basic principle that "the coronary flow is proportional to the difference in inflow and outflow pressure" is always true. The equation of FFR_{cor} might have confused the authors and led to the wrong idea that the coronary flow is proportional to the difference between the distal pressure and the wedge pressure. The authors claimed that Spaan et al [2] wrote that the coronary flow is proportional to the difference between the distal pressure and the wedge pressure, but I cannot find any sentences compatible with their claim in the paper. The authors also claimed that De Bruyne et al used the same assumption when the tandem lesion equations were derived [3], but this is also their misinterpretation. De Bruyne et al have never used the wrong idea that the coronary flow is proportional to the difference between the distal pressure and the wedge pressure, but they used the equation of FFR_{cor}. Kweon et al seem to be mistaken in their understanding of all the previous works.

Again, the equations described in the paper by Kweon et al [4] are based on the wrong idea, and need to be corrected.

Conflict of interest statement

The author has no conflicts of interest to declare.

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1. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. Circulation. 1993;87:1354-67.
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RESPONSE FROM THE ORIGINAL AUTHORS TO SAITO'S 1ST RESPONSE

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In the validation of our model, the predicted FFR values were situated within the band of true FFR±0.03 or slightly overestimated. When w=1 is used as suggested, instead of w=1.33 in our derivation, the denominator in the equation becomes larger and the predicted FFR values are further overestimated. Consequently, the outcomes will not be improved.

When the side branch flow is negligible, k becomes almost 1. To examine the equivalence, we express the prediction equations in the same manner as the conventional model in which a side branch was not taken into account [5]. When k is ~1, after stenting the distal stenosis, FFR for the remaining stenosis is

$$FFR'_{d,pred} = 1 - \Delta FFR'_{p,pred} = 1 - \frac{\Delta FFR_p}{1 - w \times \Delta FFR_d}.$$

By using the substitutions ΔFFRp=(Pa−Pm)/Pa, ΔFFRd=(Pm−Pd)/Pa and w=Pa/(Pa−Pw), it becomes

$$FFR'_{d,pred} = 1 - \frac{\frac{P_a - P_m}{P_a}}{1 - \frac{P_a}{P_a - P_w}\frac{P_m - P_d}{P_a}} = 1 - \frac{(P_a - P_w)(P_a - P_m)}{P_a(P_a - P_m + P_d - P_w)} = \frac{P_d - (P_m/P_a)P_w}{(P_a - P_m + P_d - P_w)}.$$

On the other hand, after stenting the proximal stenosis, FFR for the remaining stenosis is

$$FFR'_{d,pred} = 1 - \Delta FFR'_{d,pred} = 1 - \frac{\Delta FFR_d}{1 - w \times \Delta FFR_p}.$$

Likewise,

$$FFR'_{d,pred} = 1 - \frac{\frac{P_m - P_d}{P_a}}{1 - \frac{P_a}{P_a - P_w}\frac{P_a - P_m}{P_a}} = 1 - \frac{(P_a - P_w)(P_m - P_d)}{P_a(P_m - P_w)}.$$

Consequently, both the equations for are the same as those in the conventional model [5].

Conflict of interest statement

The authors have no conflicts of interest to declare.

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FINAL RESPONSE FROM SAITO

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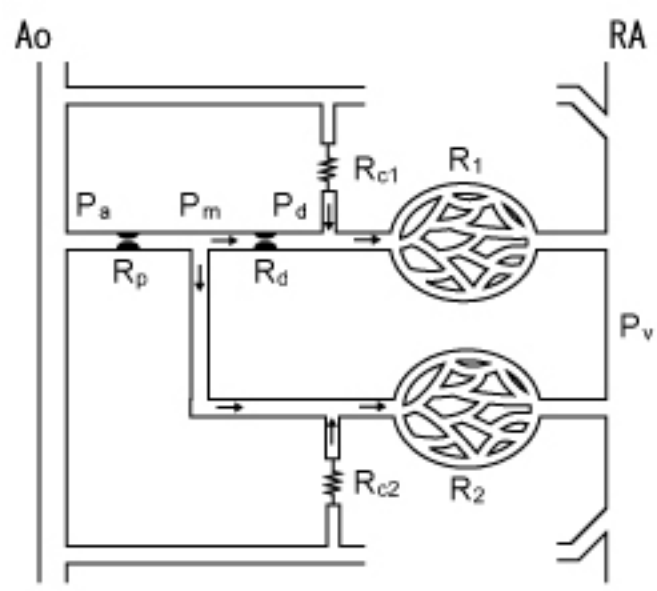
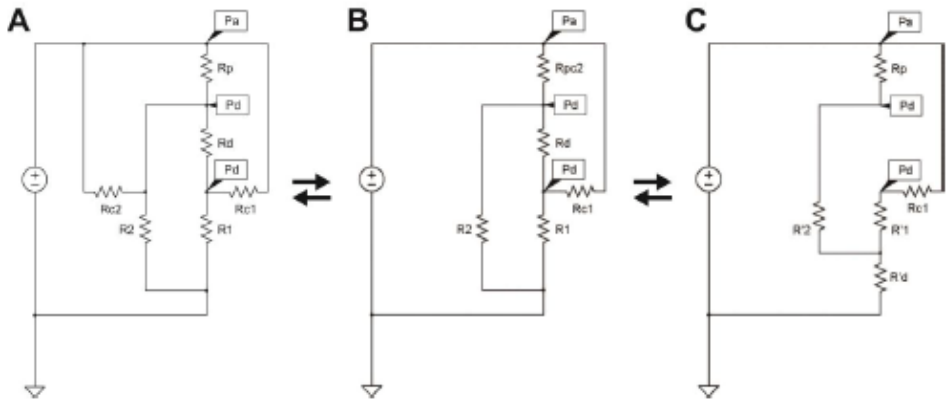
I appreciate the great efforts that the authors have made in response to my questions and concerns. The authors asserted that their equations [1] become the same equations as described in the previous work by Bruyne et al [2] when the side branch is negligible. Their claim appears to be correct. However, I am not sure that their equations are correct when the side branch is taken into account. Thus, I derived the equations by using an electric circuit model. When the pressure gradient across a pericardial stenosis is assumed to be proportional to flow, the coronary circulation can be modelled by an electric circuit.

The coronary circulation model in which a serial stenosis with an interposed side branch is depicted in **Supplementary Figure 1** and a corresponding electric circuit is depicted in **Supplementary Figure 2A**. The resistances of the proximal and distal stenosis are defined as Rp and Rd. The coronary wedge pressures in the main branch and the side branch are defined as Pw1 and Pw2 (w1=Pa/[Pa-Pw1], and w2=Pa/[Pa-Pw2]). Pw1 is not always equal to Pw2 in this model. All the other terminologies are consistent with the original paper by Kweon et al [1].



Supplementary Figure 1. A coronary circulation model in which there is a serial stenosis with an interposed side branch. In this model, coronary wedge pressure is different in the main artery and the side branch.

Rc2 and Rp are parallel-connected to each other, Rpc2 is the combined resistance of Rc2 and Rp in **Supplementary Figure 2B** (Rpc2=RpRc2/(Rp+Rc2)). Then, a delta-star transformation is applied to the delta formed by R1, R2, and Rd to simplify the calculation **(Supplementary Figure 2C)** as described in the previous study [3]. By solving circuit equations, FFRm and FFRd are expressed as in the following equations (E1 and E2).



Supplementary Figure 2.

A) Electric circuit corresponding to a coronary circulation model.

B) Equivalent circuit conversion from Figure 2A. Rpc2=Rc2*Rp/(Rc2+Rp)

C) Electric circuit obtained after the delta-star transformation. R'd=R1*R2/(R1+R2+Rd), R'1=R1*Rd/(R1+R2+Rd), R'1=R2*Rd/(R1+R2+Rd)

FFRm=((((Rd+Rc2+Rc1)*Rp+Rc2*Rd+Rc1*Rc2)*R1+Rc1*Rd*Rp+Rc1*Rc2*Rd)*R2)/(((Rd+Rc2+Rc1)*Rp+Rc2*Rd+Rc1*Rc2)*R1+(Rc1*Rd+Rc1*Rc2)*Rp+Rc1*Rc2*Rd)*R2+(Rc2*Rd+Rc1*Rc2)*Rp*R1+Rc1*Rc2*Rd*Rp) (E1)

FFRd=(((Rd+Rc2+Rc1)*Rp+Rc2*Rd+Rc1*Rc2)*R1*R2+Rc2*Rd*Rp*R1)/((((Rd+Rc2+Rc1)*Rp+Rc2*Rd+Rc1*Rc2)*R1+(Rc1*Rd+Rc1*Rc2)*Rp+Rc1*Rc2*Rd)*R2+(Rc2*Rd+Rc1*Rc2)*Rp*R1+Rc1*Rc2*Rd*Rp) (E2)

Similarly, ΔFFRp and ΔFFRd are also expressed in terms of resistance as per the following equations.

ΔFFRp

=(Rc1*Rc2*Rp*R2+(Rc2*Rd+Rc1*Rc2)*Rp*R1+Rc1*Rc2*Rd*Rp)/((((Rd+Rc2+Rc1)*Rp

+Rc2*Rd+Rc1*Rc2)*R1+(Rc1*Rd+Rc1*Rc2)*Rp+Rc1*Rc2*Rd)*R2+(Rc2*Rd+Rc1*Rc2)*Rp*R1+Rc1*Rc2*Rd*Rp) (E3)

ΔFFRd= ((Rc1*Rd*Rp+Rc1*Rc2*Rd)*R2-Rc2*Rd*Rp*R1)/((((Rd+Rc2+Rc1)*Rp+Rc2*Rd+Rc1*Rc2)*R1+(Rc1*Rd+Rc1*Rc2)*Rp+Rc1*Rc2*Rd)*R2+(Rc2*Rd+Rc1*Rc2)*Rp*R1+Rc1*Rc2*Rd*Rp) (E4)

k, w1, and w2 are also expressed in terms of resistance as per the following equations.

k=R2/(R2+R1) (E5)

1/w1=1-R1/(R1+Rc1) (E6)

1/w2=1-R2/(R2+Rc2) (E7)

The distal FFR after the treatment of the distal (FFR'm) or proximal stenosis (FFR'd) is expressed in terms of resistance in the following equations (E8 and E9).

FFR'm
=(Rp*(Rc2*R1*R2+Rc1*R1*R2)+Rc1*Rc2*R1*R2)/(Rp*(Rc2*(Rc1*(R2+R1)+R1*R2)+Rc1*R1*R2)+Rc1*Rc2*R1*R2) (E8)

FFR'd
=(Rd*R1+Rc1*R1)/(Rd*(R1+Rc1)+Rc1*R1) (E9)

By solving simultaneous quadratic equations E3 to E7, the following equations are obtained.

Rc1=-((k-1)*R2)/(k*w1-k) (E10)

Rc2=R2/w2-1 (E11)

R1=-((k-1)*R2)/k (E12)

Rd=((k-1)* ΔFFRd*R2)/(k*w1*ΔFFRp+k*w1*ΔFFRd-k) (E12)

$$Rp=-((k-1)*\Delta FFRp*R2)/(((k-1)*w2-k*w1)*\Delta FFRp-k*w1*\Delta FFRd+1) \quad (E13)$$

Substituting E10 to E13 in E8 and E9, we finally obtain:

$$FFR'm = 1-\Delta FFRp/(1-w1*k*\Delta FFRd) \quad (E14)$$

$$FFR'd = 1-\Delta FFRd/(1-w1*\Delta FFRp) \quad (E15)$$

E14 and E15 are exactly the same equations as described in the original paper by Kweon et al [1]. Interestingly, the FFR after treating the distal or proximal stenosis is independent of the coronary wedge pressure of the side branch.

I think their final equations are correct, though their derivation processes are incomprehensible. In the original paper, the authors have taken the liberty of using Pd–Pw as the driving perfusion pressure instead of Pd–Pv≈Pd, which seems to be an apparent mistake for me. However, they reached mathematically correct equations. My question is why wrongly started equations made the correct equations in the original paper [1]. I hope some smart guy will solve this puzzle.

Conflict of interest statement

The author has no conflicts of interest to declare.

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1. Kweon J, Kim YH, Yang DH, Lee JG, Roh JH, Mintz GS, Lee SW, Park SW. In vivo validation of mathematically derived fractional flow reserve for assessing haemodynamics of coronary tandem lesions. EuroIntervention. 2016;12:e1375-e1384.
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LETTER TO THE EDITOR FROM YAEGER

Letter regarding the article: “In vivo validation of mathematically derived fractional flow reserve for assessing haemodynamics of coronary tandem lesions”

A doubly stenotic artery with intermediate non-stenotic side branch is actually a three-artery configuration

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The article of Kweon et al [1] has caught my attention because they propose a model for predicting a post-stenting fractional flow reserve (FFR) of a coronary artery if either one of two serial stenoses in the artery is removed. Unlike the case of a simple single artery, the artery has a non-stenotic side branch originating from a point in-between the stenoses, turning it into a three-artery configuration.

The authors have chosen to reach their goal by modifying the classic approach to the problem of two serial stenoses in a single artery by De Bruyne et al [2]. By the errors that they have made on the way, it seems that it would have been better if they had chosen the multi-artery FFR [3] approach and treated it like a three-artery configuration (artery 1=proximal stenotic main branch; artery 2=non-stenotic side branch; artery 3=distal stenotic main branch; Figure 3 of Yaeger [3]).

Despite the different scenario, the authors seem to adhere to single artery rules. When FFR_d is <0.8 (indicating mandatory revascularisation), they compare the magnitudes of ΔFFR_p and ΔFFR_d and treat the stenosis of the higher value first (Figure 1 of Kweon et al [1]). This is erroneous because gradient pressures (ΔP_s) over stenoses can be compared only when the same flow Q passes through the resistances (R_s) of the stenoses (namely when they are in the same artery). Only then is a comparison between the gradients $\Delta P_s = Q \times R_s$ actually a comparison between the resistances (R_s). Here the flow in the proximal and distal parts of the main branch is not the same; there is a "leak" through the side branch (unless the side branch is of insignificant dimensions with negligible effect).

For some reason the authors have decided to use the diameter ratio d_2/d_1 (Figure 2 of Kweon et al [1]) for determining the ratio of blood flows of the side branch and of the distal main branch instead of using an estimated ratio of their microvascular resistances.

It is not clear why the authors are erroneously using P_d-P_w as the driving perfusion pressure instead of $P_d – P_v \approx P_d$ (P_d: distal pressure; P_w: wedge pressure; P_v: venous pressure).

It would be interesting if the authors were to run a data analysis by the multi-artery FFR method [3] and compare the results with theirs.

Conflict of interest statement

The author has no conflicts of interest to declare.

References

1. Kweon J, Kim YH, Yang DH, Lee JG, Roh JH, Mintz GS, Lee SW, Park SW. In vivo validation of mathematically derived fractional flow reserve for assessing haemodynamics of coronary tandem lesions. EuroIntervention. 2016;12:e1375-e1384.

2. 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.

3. Yaeger IA. A multi-artery Fractional Flow Reserve (FFR) approach for handling coronary stenosis-stenosis interaction in the multi-vessel disease (MVD) arena. Int J Cardiol. 2016;203:807-15.

REPLY TO THE LETTER TO THE EDITOR FROM YAEGER

Reply to the letter to the editor by Yaeger regarding the article "In vivo validation of mathematically derived fractional flow reserve for assessing haemodynamics of coronary tandem lesions"

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We appreciate the interest in our article [1]. The author raised the issues of the driving force for myocardial flow, the flow ratio estimation, and the procedural order. Also, the author suggested that the application of the prediction model in Yaeger [2] would improve the outcomes of FFR prediction.

Spaan et al [3] showed that, even without collateral flows, $(P_d-P_v)/(P_a-P_v)$ overestimates the coronary flow ratio (Q_S/Q_N) and the microvascular resistance (R_{min}) increases as the distal pressure (P_d) falls. To build an equation to describe the P-Q relationship better, we introduced "R" corresponding to the inverse of the slope for Q vs. P_d-P_w, instead of using a constant microvascular resistance (Figure 4 in Spaan et al [3]). The flow ratios to branches, in the same regard, were estimated using anatomical metrics. Because "R" in our mathematical derivation is dimensionally equivalent to the resistance in electronic circuit modelling, we called it "resistance".

For determining the procedural order, previous studies have recommended that treatment of the stenosis with greater pressure or FFR gradient during pressure wire pullback should be prioritised [4], as addressed in the introduction of our article [1]. Please remember that the objective of our work was to propose a better method for predicting more severe lesions.

The prediction model of Yaeger [2] was examined and the outcomes are listed in **Table 1**. The mean error was 0.057±0.059 and the mean absolute error was 0.063±0.052. In the **Appendix** please find the translation of Yaeger's prediction model [2] to the notations in our derivation.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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1. Kweon J, Kim YH, Yang DH, Lee JG, Roh JH, Mintz GS, Lee SW, Park SW. In vivo validation of mathematically derived fractional flow reserve for assessing haemodynamics of coronary tandem lesions. EuroIntervention. 2016;12:e1375-e1384.

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Table 1. Validation data set.

Patient number	Lesion	Treatment	Measured before intervention			Measured after the first intervention	Estimated flow ratio	Predicted		
			FFR_prox	FFR_mid	FFR_dist	FFR_dist	k	conventional model	current model	Yaeger's model
1	LCX	distal	1	0.94	0.75	0.92	0.81	0.92	0.92	0.93
2	LAD	proximal	1	0.35	0.29	0.52	0.94	0.55	0.55	0.83
3	RCA	proximal	0.95	0.74	0.66	0.75	0.86	0.88	0.84	0.89
4	RCA	proximal	1	0.81	0.76	0.91	0.96	0.93	0.93	0.94
5	LAD	distal	0.92	0.83	0.71	0.77	0.97	0.84	0.81	0.82
6	LAD	proximal	0.93	0.81	0.73	0.85	0.76	0.89	0.83	0.90
7	LAD	distal	0.82	0.73	0.52	0.71	0.60	0.67	0.71	0.70
8	LAD	distal	0.97	0.87	0.6	0.75	0.95	0.80	0.82	0.85
9	LAD	distal	0.97	0.81	0.6	0.78	0.84	0.74	0.76	0.79
10	LAD	proximal	0.95	0.86	0.71	0.78	0.91	0.82	0.78	0.83
11	LAD	proximal	0.95	0.82	0.78	0.91	0.91	0.95	0.90	0.95
12	LAD	distal	1	0.95	0.47	0.94	0.78	0.86	0.90	0.93
13	LAD	distal	1	0.89	0.68	0.82	0.93	0.85	0.85	0.88
14	LAD	proximal	0.95	0.81	0.71	0.81	0.82	0.87	0.83	0.88
15	LAD	distal	1	0.89	0.75	0.84	0.87	0.86	0.87	0.88
16	LAD	distal	1	0.93	0.55	0.81	0.96	0.86	0.86	0.91
17	LAD	proximal	1	0.77	0.69	0.85	0.66	0.88	0.88	0.90
18	LAD	distal	1	0.92	0.63	0.86	0.78	0.87	0.89	0.91
19	RCA	proximal	1	0.63	0.61	0.94	0.99	0.96	0.96	0.97
20	RCA	distal	0.95	0.93	0.67	0.84	0.94	0.89	0.92	0.92
21	LAD	distal	1	0.69	0.61	0.78	0.71	0.86	0.86	0.68
22	LAD	proximal	1	0.82	0.76	0.88	0.75	0.92	0.92	0.93
23	LAD	distal	1	0.87	0.76	0.85	0.61	0.85	0.86	0.86
24	LAD	distal	0.94	0.84	0.75	0.86	0.83	0.82	0.83	0.83
25	RCA	proximal	0.98	0.74	0.7	0.90	0.85	0.94	0.92	0.95
26	LAD	proximal	0.99	0.7	0.59	0.76	0.88	0.82	0.81	0.84
27	LAD	distal	0.95	0.88	0.72	0.86	0.88	0.85	0.86	0.87
28	RCA	distal	1	0.8	0.52	0.68	0.90	0.68	0.70	0.77
29	LAD	proximal	0.94	0.7	0.58	0.71	0.82	0.80	0.76	0.83
30	RCA	distal	0.96	0.94	0.56	0.92	0.94	0.88	0.92	0.93
31	LAD	proximal	0.98	0.76	0.72	0.90	0.82	0.94	0.92	0.95
32	LAD	distal	0.94	0.89	0.75	0.85	0.80	0.86	0.88	0.88
33	RCA	proximal	0.94	0.8	0.75	0.88	0.75	0.93	0.88	0.94
34	LAD	proximal	1	0.78	0.69	0.85	0.86	0.87	0.87	0.88
35	RCA	proximal	0.93	0.83	0.76	0.77	0.77	0.91	0.85	0.92
36	LAD	proximal	1	0.84	0.72	0.83	0.80	0.85	0.85	0.86
37	LAD	proximal	0.95	0.76	0.69	0.84	0.72	0.90	0.86	0.91
38	LAD	proximal	0.94	0.71	0.65	0.77	0.68	0.90	0.85	0.92
39	LAD	distal	0.91	0.73	0.41	0.63	0.79	0.53	0.64	0.68
40	LAD	distal	0.95	0.82	0.75	0.82	0.74	0.80	0.81	0.81
41	RCA	distal	1	0.89	0.73	0.85	0.94	0.86	0.86	0.88
42	RCA	distal	0.92	0.87	0.3	0.76	0.90	0.46	0.76	0.82
43	LAD	proximal	1	0.84	0.71	0.74	0.57	0.83	0.83	0.85
44	LAD	proximal	0.98	0.84	0.77	0.84	0.70	0.91	0.89	0.92
45	LAD	distal	1	0.88	0.73	0.82	0.79	0.85	0.86	0.87
46	RCA	proximal	1	0.84	0.77	0.88	0.87	0.91	0.91	0.92
47	LAD	proximal	0.98	0.86	0.76	0.84	0.90	0.88	0.86	0.88
48	LAD	proximal	1	0.74	0.6	0.73	0.72	0.79	0.79	0.81
49	LAD	proximal	1	0.81	0.77	0.84	0.72	0.95	0.95	0.95
50	LAD	proximal	0.97	0.83	0.74	0.79	0.75	0.88	0.86	0.89

Appendix. Translation of Yaeger's prediction model to the notations in the derivation by Kweon et al.

For simplicity, abbreviations are used as follows.

$FFR^{app}(LM) = a$

$FFR^{true}(LM) = b$

$FFR^{app}(LAD) = FFR^{true}(LAD) = c$ Eq (*1)

$FFR^{real}(LM) = d$

$FFR^{real}(LAD) = e$

From the pullback measurement, $FFR^{app}(LM)$ and $FFR^{app}(LAD)$ are obtained. For the comparison with our mathematical model, we rephrased the equations in Yaeger [2] as functions of “a” and “c” as follows.

Equation (19) in Yaeger [2] is

$$FFR^{app}(LM) = \frac{1}{0.5\times\left[1-FFR^{true}(LM)\right]\left[1+FFR^{true}(LAD)\right]/FFR^{true}(LM)+1}.$$

Using the abbreviations above, it becomes

$$a = \frac{1}{0.5\times(1-b)(1+c)/b+1}. \quad \text{Eq (*2)}$$

By multiplying both numerator and denominator by 2b, we can get

$$a = \frac{2b}{(1-b)(1+c)+2b} = \frac{2b}{1-b+c-bc+2b} = \frac{2b}{1+b+c-bc}.$$

By multiplying both sides by the denominator, it becomes

$a(1+b+c-bc) = 2b$ and $a(1+c) = b(ac-a+2)$.

Subsequently, b can be expressed as

$$b = \frac{a(c+1)}{a(c-1)+2}. \quad \text{Eq (*3)}$$

Equation (23) in Yaeger [2] is

$$FFR^{real}(LM) = \frac{1-FFR^{app}(LM)}{1-FFR^{true}(LM)}\times FFR^{true}(LM).$$

Using the abbreviations above, it becomes

$$d = \frac{1-a}{1-b}\times b.$$

Using the expression in Eq (*3), we can get

$$d = \frac{1-a}{1-\frac{a(c+1)}{a(c-1)+2}} \times \frac{a(c+1)}{a(c-1)+2} = \frac{(1-a)a(c+1)}{a(c-1)+2-a(c+1)} = \frac{(1-a)a(c+1)}{2(1-a)} = \frac{a(c+1)}{2}.$$

Using the notations in Yaeger [2], the prediction equation for LAD treatment becomes

$$FFR^{real}(LM) = \frac{FFR^{app}(LM)\left[FFR^{true}(LAD)+1\right]}{2}.$$

Equation (34) for the LM treatment in Yaeger [2] is

$$FFR^{real}(LAD) = \frac{FFR^{true}(LAD)}{0.5\times\left[1/FFR^{true}(LM)-1\right]\left[1+FFR^{true}(LAD)\right]+1}.$$

Using the abbreviations above, it becomes

$$e = \frac{c}{0.5\times(1/b-1)(1+c)+1}.$$

Using the expression in Eq (*2), we can get

$e = ac$.

Using the notations in Yaeger [2], the prediction equation for LM treatment becomes

$$FFR^{real}(LAD) = FFR^{app}(LM)\times FFR^{true}(LAD).$$

Using the notations in our derivation, the equations above are translated as follows.

Eq (*1) $\rightarrow$ $FFR'_{d,pred} = \frac{FFR_d}{FFR_m}$ for proximal treatment

Eq (*3) $\rightarrow$ $FFR'_{d,pred} = \frac{FFR_d + FFR_m}{FFR_d - FFR_m + 2}$ for distal treatment

FINAL RESPONSE FROM YAEGER

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The authors of the article [1] steadfastly cling to the basic single-artery FFR approach in an attempt to account for stenosis-stenosis interaction in an arterial configuration that extends beyond the frame of a single artery. There is a stenosis-free side branch emerging from a point in-between two stenoses of an artery and this spoils the single-artery picture. The side branch thus turns the single artery into a virtually equivalent three-artery configuration ([stenotic first part of main artery]-[stenosis-free side branch]-[stenotic remainder of main artery]) that the basic FFR approach cannot and has never been designed to handle [2].

In their article [1], the authors occasionally abandon the basic pressure-resistance-flow scheme and employ parts of some other approaches. As indicated by Dr Saito and myself, for no apparent theoretical reason, the authors have taken the liberty of using $P_d–P_w$ as the driving perfusion pressure instead of $P_d–P_v≈P_d$ (P_d: distal pressure; P_w: wedge pressure; P_v: venous pressure). Also, they correlate the flows of the side branch and the distal main artery through their diametrical ratios instead of relating the flows to pressures and stenotic resistances. Furthermore, they use the pullback method in the main artery and give revascularisation priority to the stenosis with the higher-pressure gradient (for some reason, they denote it ΔFFR instead of ΔP) despite the fact that this is correct for tandem stenoses only in a single artery. In reference 3 of the article by Kweon et al, it is clearly indicated that in “tandem lesions” the authors refer to “2 stenoses along 1 coronary artery” [3]. Also, “lesions with large side branches between the stenoses and the left main coronary artery stenosis” [3] were excluded from the clinical study (namely, it seems that this kind of revascularisation prioritising is valid only if the side branches are negligible, but the authors fail to mention it).

Conflict of interest statement

The author has no conflicts of interest to declare.

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1. Kweon J, Kim YH, Yang DH, Lee JG, Roh JH, Mintz GS, Lee SW, Park SW. In vivo validation of mathematically derived fractional flow reserve for assessing haemodynamics of coronary tandem lesions. EuroIntervention. 2016;12:e1375-e1384.
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INVITED EXPERT'S COMMENTS

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I have tried to read and understand the paper by Kweon et al again, but again I found a number of issues which are disputable. I understand the objections by Dr Saito and Dr Yaeger.

What I notice is the following:

1. In the paper, the definition of the resistances R1 and R2 is vague and unclear.

What does it mean? Is it the stenosis itself? In that case, I can at least understand why the authors use Pa-Pw (although that might be wrong because the gradient across the epicardial lesion is not linearly related to flow in contrast to the myocardium).

Fundamentally, however, myocardial flow is (at maximum vasodilation) determined by the driving pressure Pd-Pv, as stated by Dr Saito.

If, by R1 and R2, the authors mean the epicardial resistance, one can wonder at the relevance of their work because measuring indices for coronary flow is not representative of myocardial flow, at least not in the case of serial stenosis, and therefore limited for decision making.

2. It is unclear what the justification is to presume that Pw is equal for the side branch and the main branch.

3. Similarly, it is a crude assumption that Pw equals 25 mmHg.

In very large series in our lab, average Pw is indeed around 23 mmHg.
However, the variation is tremendous (from 5-65 mmHg).

4. Another assumption made (which has nothing to do with the mathematics) is the use of QCA at the bifurcation for estimating flow scaling (parameter k).

We all know the serious shortcomings of QCA and difficulties of obtaining exact geometric information from angiography, not to mention deriving physiology from anatomy.

5. A good, valid and complete mathematical description should also be true in case of substituting the (extreme) boundary values, representing a completely normal artery (either without intervention or after stenting) and a complete occlusion (either before or after stenting) of one or both of the tandem lesions.

In the mathematical model on tandem lesions described by De Bruyne et al [1], that is explicitly the case and verified.

Also, in the first paper by Pijls et al, introducing the concept of FFR [2], you see that all formulas and equations remain valid at extreme values.

For the equations by Kweon et al, that does not seem to be the case.

In fact, the paper of Kweon is not a “full mathematical description” (like the FFR description in the 1993 Circulation paper or the tandem mathematics in the 2000 Circulation paper), but a model with several assumptions and hypotheses.

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RESPONSE BY KWEON ET AL TO THE INVITED EXPERT

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Expert comments

1. In the paper, the definition of the resistances R1 and R2 is vague and unclear. What does it mean? Is it the stenosis itself? In that case, I can at least understand why the authors use Pa-Pw (although that might be wrong because the gradient across the epicardial lesion is not linearly related to flow (in contrast to the myocardium). Fundamentally, however, myocardial flow is (at maximum vasodilation) determined by the driving pressure Pd-Pv, as stated by Dr Saito.
If, by R1 and R2, the authors mean the epicardial resistance, one can wonder at the relevance of their work because measuring indices for coronary flow is not representative of myocardial flow, at least not in the case of serial stenosis, and therefore limited for decision making.

< Answer >
Spaan et al [1] showed that, even without collateral flows, $(P_d-P_v)/(P_a-P_v)$ overestimates the coronary flow ratio (Q_S/Q_N), and the microvascular resistance (R_{min}) increases as the distal pressure (P_d) falls. To build an equation to describe the P-Q relationship better, we introduced "R" corresponding to the inverse of the slope for Q vs. P_d-P_w, instead of using a constant microvascular resistance (see Figure 4 in Spaan et al [1]). Because "R" in our mathematical derivation is dimensionally equivalent to the resistance in electronic circuit modelling, we called it "resistance".

Please check the derivation below, which was included in the original submission. Our prediction model for distal treatment, which is independent of side branches, is equivalent to the "conventional model" [2]. When the flow to interposed side branches is negligible or absent ($k\approx1$), our prediction model for proximal treatment is also equivalent to the "conventional model". These are associated with the P-Q relationship considered in our derivation, which is consistent with the definition of fractional coronary artery flow reserve [3] used in the mathematical derivation of the "conventional model". Following the notations of Pijls et al [3],

$$FFR_{cor} = \frac{Q_s}{Q_s^N} = \frac{P_d - P_w}{P_a - P_w}$$

$$\Rightarrow Q_s = \frac{Q_s^N}{P_a - P_w}(P_d - P_w) \sim (P_d - P_w).$$

As you noticed, many of the assumptions and equations for the derivation of the "conventional model" were used for our mathematical derivation, and thus we called the prediction model "conventional" with great respect. Consequently, our mathematical model is not consistent with the model in Yamamoto et al [4], as stated by Dr Saito, but is consistent with the "conventional model". To show the equivalence explicitly and clearly, we included the derivation below in the supplementary material. However, after the first revision, in order to follow the new editorial policy of EuroIntervention which does not allow supplementary materials, it was removed. We hope this situation is understood.

When the side branch flow is negligible, k becomes almost 1. To examine the equivalence, we express the prediction equations in the same manner as the conventional model in which a side branch was not taken into account [2]. When k is ~1, after stenting the distal stenosis, FFR for the remaining stenosis is

$$FFR'_{d,pred} = 1 - \Delta FFR'_{p,pred} = 1 - \frac{\Delta FFR_p}{1 - w \times \Delta FFR_d}.$$

By using the substitutions $\Delta FFR_p=(P_a-P_m)/P_a$, $\Delta FFR_d=(P_m-P_d)/P_a$ and $w=P_a/(P_a-P_w)$, it becomes

$$FFR'_{d,pred} = 1 - \frac{\frac{P_a - P_m}{P_a}}{1 - \frac{P_a}{P_a - P_w}\frac{P_m - P_d}{P_a}} = 1 - \frac{(P_a - P_w)(P_a - P_m)}{P_a(P_a - P_m + P_d - P_w)} = \frac{P_d - (P_m/P_a)P_w}{(P_a - P_m + P_d - P_w)}.$$

On the other hand, after stenting the proximal stenosis, FFR for the remaining stenosis is

$$FFR'_{d,pred} = 1 - \Delta FFR'_{d,pred} = 1 - \frac{\Delta FFR_d}{1 - w \times \Delta FFR_p}.$$

Likewise,

$$FFR'_{d,pred} = 1 - \frac{\frac{P_m - P_d}{P_a}}{1 - \frac{P_a}{P_a - P_w}\frac{P_a - P_m}{P_a}} = 1 - \frac{(P_a - P_w)(P_m - P_d)}{P_a(P_m - P_w)}.$$

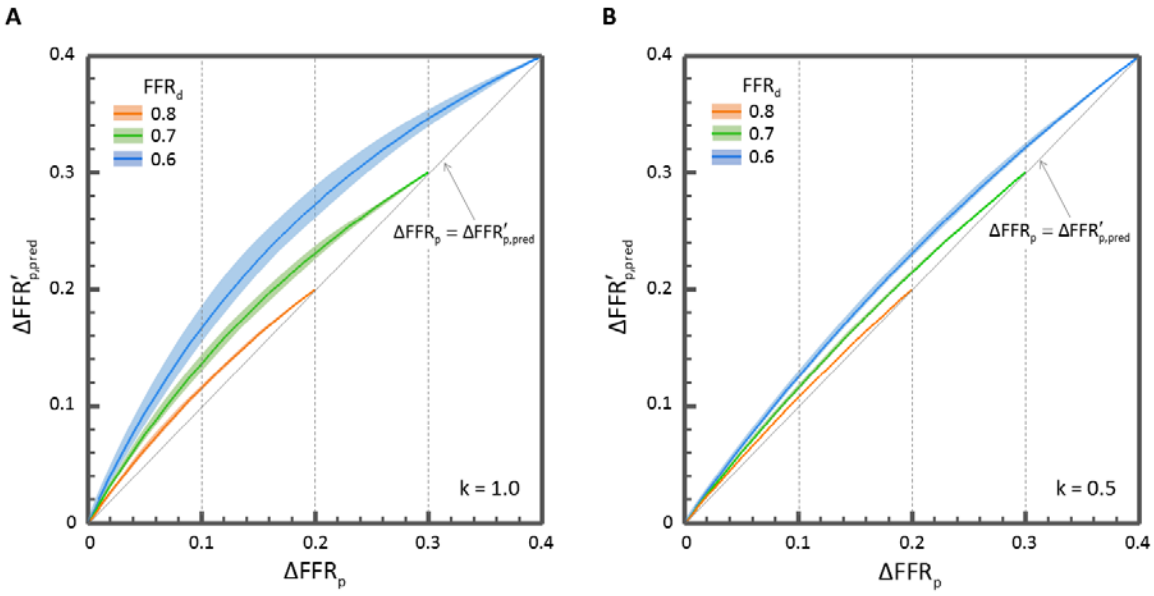
Consequently, both the equations for $FFR'_{d,pred}$ are the same as those in the conventional model [2].

2. It is unclear what the justification is to presume that Pw is equal for the side branch and the main branch.

3. Similarly, it is a crude assumption that Pw equals 25 mmHg.
In very large series in our lab, average Pw is indeed around 23 mmHg.
However, the variation is tremendous (from 5-65 mmHg).

<Answer>
The measurement of wedge pressure in the conventional model of De Bruyne et al [2] was indicated as an essential component of the FFR prediction, because it varies with individuals and vessel segments as noted. However, despite the sophisticated modelling and high accuracy of the conventional model, it has been the primary constraint to prevent the widespread application of the model due to the time requirement and lesion damage in the measurement procedure. To resolve this issue, we set the ratio of wedge pressure to aortic pressure (P_w/P_a=0.25) as a fixed value based on the previous reports and evaluated the uncertainty associated with the wedge pressure. When both the proximal and distal stenoses reached the PCI criterion ($\Delta FFR_p=\Delta FFR_d=0.2$), the estimated discrepancy of the predicted FFR was $\leq$0.02 within the range of $0\leq P_w/P_a\leq 0.39$. Initial data (four patients) also had an error of $\leq$0.01 between the FFR values predicted with the assumed and the measured wedge pressures (distal main branch). This result indicated that the approximated wedge pressure did not severely hamper the prediction capability of our current model. In the same regard, the difference in the wedge pressures of side and distal main branches would not produce a large amount of error. We will provide the uncertainty analysis associated with the different wedge pressures for the side and distal main branches, if you wish. The bias caused by assuming wedge pressures is presented as a limitation of our current analysis.

In the original submission, the uncertainty quantification associated with wedge pressures was included but it was removed to follow the new editorial policy of EuroIntervention. Please find it below **(Supplementary Figure 3)**.



Supplementary Figure 3. Uncertainty of $\Delta FFR'_{p,pred}$ associated with the wedge pressure for $FFR_d=1-\Delta FFR_p-\Delta FFR_d$ =0.6, 0.7 and 0.8. Coloured solid line denotes P_w/P_a=0.25 and the shaded region indicates the variations in $\Delta FFR'_{p,pred}$ whose upper and low boundaries correspond to P_w/P_a=0.35 and 0.15, respectively.

A) Negligible side branch (k=1).

B) Large side branch (k=0.5). With a negligible side branch (k=1.0), the maximum discrepancy was −0.013–0.019 (ΔFFR_p=0.12, and ΔFFR_d=0.28), while with a large side branch (k=0.5), the maximal discrepancy was −0.004–0.006 (ΔFFR_p=0.14, and ΔFFR_d=0.26).

FFR: fractional flow reserve; ΔFFR_p and ΔFFR_d: FFR gradients over proximal and distal stenoses, respectively; k: flow fraction of main branch at bifurcation point of interest; P_a: mean aortic pressure; P_w: mean wedge pressure; pred: predicted; ′: after treatment of a stenosis

4. Another assumption made (which has nothing to do with the mathematics) is the use of QCA at the bifurcation for estimating flow scaling (parameter k).
We all know the serious shortcomings of QCA and difficulties of obtaining exact geometric information from angiography, not to mention deriving physiology from anatomy.

<Answer>

We agree about the concerns about the accuracy and reproducibility of QCA. For more rigorous validation, direct measurements of the flow rate to each branch would be better. Instead, we estimated the uncertainty produced by misestimation of the diameter ratio and thereby the flow rate. Figure 4A in our published paper shows that, when k is misestimated by 0.1, the associated prediction error becomes $\leq$0.01 for the lesion with FFR_d >0.6. This implies that the k value obtained with a rough estimation using Figure 2 in our published paper does not hamper the prediction accuracy. Therefore, the real-time application of our prediction model using QCA is feasible in the clinical situation.

5. A good, valid and complete mathematical description should also be true in case of substituting the (extreme) boundary values, representing a completely normal artery (either without intervention or after stenting) and a complete occlusion (either before or after stenting) of one or both of the tandem lesions.
In the mathematical model on tandem lesions described by De Bruyne et al [2], that is explicitly the case and verified.
Also, in the first paper by Pijls et al, introducing the concept of FFR [3], you see that all formulas and equations remain valid at extreme values.
For the equations by Kweon et al, that does not seem to be the case.
In fact, the paper of Kweon is not a "full mathematical description" (like the FFR description in the 1993 Circulation paper or the tandem mathematics in the 2000 Circulation paper), but a model with several assumptions and hypotheses.

<Answer>
When one of the serial stenoses is absent, FFR values are correctly predicted, as shown in **Supplementary Table 1**. For a complete occlusion, our prediction model gives $FFR'_{d,pred}$=0.25 because we assumed P_w/P_a=0.25 for simplicity. On the other hand, when the distal lesion totally occluded is treated, our prediction model can be used to estimate the post-stenting FFR gradient as $\Delta FFR_p/(1-k)$. When k=1 (no interposed side branch), our prediction model is essentially consistent with the conventional model, as addressed above. We believe that, in the clinical context, the benefit of our prediction model free from wedge pressure measurements is greater than the drawback of prediction errors for the total occlusion lesion, to which FFR measurement is not routinely applied, and that our prediction model provides an insight into physiological understanding including complete occlusions.

Supplementary Table 1.

	Proximal stenting	Distal stenting
No proximal stenosis $\Delta FFR_p = 0$	$1-\Delta FFR_d$ $(= P_d/P_a)$	1
No distal stenosis $\Delta FFR_d = 0$	1	$1-\Delta FFR_p$ $(= P_m/P_a = P_d/P_a)$

In the original submission, the full mathematical description was included as supplementary material. As noted above, after the first revision, in accordance with the new editorial policy of EuroIntervention, it was summarised as shown and the reviewers agreed. We hope you understand the situation. Please find the full description of the mathematical derivation in the **Supplementary Appendix**. In addition, the derivation for the tandem lesion with multiple side branches, which a reviewer asked to be revised, is presented below.

Derivation for tandem lesion with multiple bifurcations.

When *n* side branches are interposed between stenoses, the sum of flow rates to the side branches becomes

$$Q_{t2} = \sum_{i=1}^{n}\left(P_m - P_w\right)/R_{2i} \text{ and } Q_{p2} = \sum_{i=1}^{n}\left(P'_m - P'_w\right)/R_{2i}$$

before and after stenting the distal stenosis, respectively, where R_{2i} is the resistance of the *i*th side branch. The linear relationship between the flow rate and the pressure drop over the proximal stenosis yields

$$\frac{P_a - P_m}{P'_a - P'_m} = \frac{Q_t}{Q_p} = \frac{Q_{t1}+Q_{t2}}{Q_{p1}+Q_{p2}} = \frac{\left(P_d - P_w\right)/R_1 + \sum_{i=1}^{n}\left(P_m - P_w\right)/R_{2i}}{\left(P'_m - P'_w\right)/R_1 + \sum_{i=1}^{n}\left(P'_m - P'_w\right)/R_{2i}},$$

as the modified form of the equation (E1). By dividing with P_a/P'_a and using the substitutions $P_d/P_a=1-\Delta FFR_p-\Delta FFR_d$, $P_m/P_a=1-\Delta FFR_p$ and $P'_m/P'_a=1-\Delta FFR'_p$, it becomes

$$\frac{\Delta FFR_p}{\Delta FFR'_p} = \frac{\left(1-\Delta FFR_p-\Delta FFR_d\right)/R_1 + \sum_{i=1}^{n}\left(1-\Delta FFR_p\right)/R_{2i} - P_w/P_aR_1 - \sum_{i=1}^{n}P_w/P_aR_{2i}}{\left(1-\Delta FFR'_p\right)/R_1 + \sum_{i=1}^{n}\left(1-\Delta FFR'_p\right)/R_{2i} - P'_w/P'_aR_1 - \sum_{i=1}^{n}P'_w/P'_aR_{2i}}.$$

For simplicity, we define two coefficients as

$$C_1 = \left(1/R_1 + \sum_{i=1}^{n} 1/R_{2i}\right)\left(1 - P_w/P_a\right) = \left(1/R_1 + \sum_{i=1}^{n} 1/R_{2i}\right)\left(1 - P'_w/P'_a\right)$$

and

$$C_2 = 1/R_1 + \sum_{i=1}^{n} 1/R_{2i}\,.$$

Using C_1 and C_2, we can obtain

$$\frac{\Delta FFR_p}{\Delta FFR'_p} = \frac{C_1 - C_2 \Delta FFR_p - \Delta FFR_d / R_1}{C_1 - C_2 \Delta FFR'_p}.$$

Rearrangement of the equation gives

$$\Delta FFR'_p = \frac{\Delta FFR_p}{1 - \Delta FFR_d / R_1 C_1},$$

which is identical to the equation (E3).

When we consider the sum of flow rates to the side branches in an ideal condition as the equation (E6), it becomes

$$Q_2 = \sum_{i=1}^{n} \left(P''_a - P''_w\right)/R_{2i}\,.$$

The resistance term in coefficients C_1 and C_2 can be expressed as

$$1/R_1 + \sum_{i=1}^{n} 1/R_{2i} = \frac{Q_1 + Q_2}{P''_a - P''_w} = \frac{Q_0}{P''_a - P''_w},$$

and C_1 becomes

$$C_1 = \frac{Q_0}{P''_a - P''_w}\frac{P''_a - P''_w}{P''_a} = \frac{Q_0}{P''_a}.$$

Because the coefficient C_1 is the same as that in the derivation for single bifurcations, we can finally obtain the identical expression with the equation (E7).

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary Appendix. Mathematical derivation.

A. Flow rate estimation using resistance model

Online Figure 1 shows serial stenoses with an interposed side branch. Because the pressure drop on a normal lesion is negligible [1,2], the distal pressures of the main and side branches are P_d and P_m, respectively. At maximum vasodilation, the flow rate to each branch is proportional to the difference between the distal pressure and the wedge pressure P_w. The P_w is assumed to be the same for the main and side branches. By introducing a resistance, the flow rates to the main and side branches are defined as

$$Q_{t1} = \left(P_d - P_w\right) / R_1$$

and

$$Q_{t2} = \left(P_m - P_w\right) / R_2 ,$$

respectively. R_1 and R_2 are the inverses of the proportional coefficients between the flow rate and the pressure difference for the main and side branches, respectively.

When a percutaneous coronary intervention is performed on the distal stenosis, as shown in **Online Figure 1B**, the proximal and distal pressures to the remaining stenosis are changed to P'_a and P'_m, respectively. The flow rates to the main and side branches become

$$Q_{p1} = \left(P'_m - P'_w\right) / R_1$$

and

$$Q_{p2} = \left(P'_m - P'_w\right) / R_2 ,$$

respectively, where P'_w is the wedge pressure after stenting the distal stenosis.

Likewise, after treating the proximal stenosis, as shown in **Online Figure 1C**, the distal pressure to the remaining stenosis is changed to P'_d. Correspondingly, the flow rate to the main branch becomes

$$Q_{d1} = \left(P'_d - P'_w\right) / R_1 .$$

B. Prediction of FFR gradient after stenting distal stenosis

To predict $\Delta FFR'_p$, the FFR gradient over the proximal stenosis after stenting the distal stenosis, it is assumed that the linear relationship exists between the flow rate and the pressure gradient over the proximal stenosis. That is,

$$\frac{P_a - P_m}{P'_a - P'_m} = \frac{Q_t}{Q_p} = \frac{Q_{t1} + Q_{t2}}{Q_{p1} + Q_{p2}} = \frac{\left(P_d - P_w\right) / R_1 + \left(P_m - P_w\right) / R_2}{\left(P'_m - P'_w\right) / R_1 + \left(P'_m - P'_w\right) / R_2},$$

where Q_t and Q_p are the flow rates over the proximal stenosis pre- and post-stenting, respectively. By dividing with P_a/P'_a and using the substitutions $P_d/P_a=1-\Delta FFR_p-\Delta FFR_d$, $P_m/P_a=1-\Delta FFR_p$ and $P'_m/P'_a=1-\Delta FFR'_p$, it becomes

(E1) $$\frac{\Delta FFR_p}{\Delta FFR'_p} = \frac{\left(1-\Delta FFR_p-\Delta FFR_d\right) / R_1 + \left(1-\Delta FFR_p\right) / R_2 - P_w / P_a R_1 - P_w / P_a R_2}{\left(1-\Delta FFR'_p\right) / R_1 + \left(1-\Delta FFR'_p\right) / R_2 - P'_w / P'_a R_1 - P'_w / P'_a R_2},$$

where ΔFFR_p and ΔFFR_d are the FFR gradients over the proximal and distal stenoses before the treatment.

For simplicity, we define two coefficients as

(E2) $$C_1 = \left(1/R_1 + 1/R_2\right)\left(1 - P_w / P_a\right) = \left(1/R_1 + 1/R_2\right)\left(1 - P'_w / P'_a\right)$$

and

$$C_2 = 1/R_1 + 1/R_2 .$$

For C_1, the relationship between the aortic and wedge pressures using the central venous pressure (P_v) [1] is approximated as $(P_w-P_v)/(P_a-P_v)\approx P_w/P_a$=constant, as used in the conventional model [3]. That is, $P_w/P_a = P'_w/P'_a$.

Using C_1 and C_2, equation (E1) is expressed as

$$\frac{\Delta FFR_p}{\Delta FFR'_p} = \frac{C_1 - C_2 \Delta FFR_p - \Delta FFR_d / R_1}{C_1 - C_2 \Delta FFR'_p}.$$

By multiplying $(C_1 - C_2\,\Delta FFR'_p)/\Delta FFR_p$, it becomes

$$\frac{C_1}{\Delta FFR'_p} - C_2 = \frac{C_1 - \Delta FFR_d / R_1}{\Delta FFR_p} - C_2 .$$

By cancelling C_2 and taking the inverse, we obtain

(E3) $$\Delta FFR'_p = \frac{\Delta FFR_p}{1 - \Delta FFR_d / R_1 C_1} .$$

C. Prediction of FFR gradient after stenting proximal stenosis

For the prediction of $\Delta FFR'_d$, the linear relationship between the flow rate and the pressure drop over the distal stenosis yields

$$\frac{P_m - P_d}{P'_a - P'_d} = \frac{Q_{t1}}{Q_{d1}} = \frac{(P_d - P_w)/R_1}{(P'_d - P'_w)/R_1} .$$

By dividing with P_a/P'_a and using the substitutions $P_d/P_a = 1 - \Delta FFR_p - \Delta FFR_d$, $P_m/P_a = 1 - \Delta FFR_p$ and $P'_d/P'_a = 1 - \Delta FFR'_d$, it becomes

(E4) $$\frac{\Delta FFR_d}{\Delta FFR'_d} = \frac{1 - \Delta FFR_p - \Delta FFR_d - P_w / P_a}{1 - \Delta FFR'_d - P'_w / P'_a} .$$

For simplicity, we define a coefficient as

$$C_3 = 1 - P_w / P_a = 1 - P'_w / P'_a .$$

and equation (E4) becomes

$$\frac{\Delta FFR_d}{\Delta FFR'_d} = \frac{C_3 - \Delta FFR_p - \Delta FFR_d}{C_3 - \Delta FFR'_d} .$$

Rearrangement of the equation gives

$$\frac{C_3}{\Delta FFR'_d} - 1 = \frac{C_3 - \Delta FFR_p}{\Delta FFR_d} - 1 .$$

Therefore,

(E5) $$\Delta FFR'_d = \frac{\Delta FFR_p}{1 - \Delta FFR_d / C_3} .$$

D. Prediction model using clinical measurements

For the prediction of $\Delta FFR'_p$ and $\Delta FFR'_d$ after a treatment, we define the coefficients which include clinically infeasible parameters, such as R_1 and R_2. To estimate these quantities, the coronary bifurcation after stenting both stenoses is taken into account, as shown in **Online Figure 1D**. In an ideal situation, the distal pressure of the main and side branches is recovered to P_a^0, the same as the mean aortic pressure. Therefore, the flow rates to the main and side branches are

$$Q_1 = \left(P_a^0 - P_w^0\right) / R_1$$

and

$$Q_2 = \left(P_a^0 - P_w^0\right) / R_2,$$

Respectively; P_w^0 is the corresponding wedge pressure. By substituting Q_1 and Q_2 into equation (E2), R_1 and R_2 can be eliminated and as a consequence,

$$C_1 = \frac{Q_1 + Q_2}{P_a^0 - P_w^0}\left(1 - P_w / P_a\right) = \frac{Q_1 + Q_2}{P_a^0 - P_w^0}\left(1 - P_w^0 / P_a^0\right).$$

By multiplying R_1 and taking the inverse,

$$\frac{1}{R_1 C_1} = \frac{Q_1}{P_a^0 - P_w^0}\frac{P_a^0 - P_w^0}{Q_1 + Q_2}\frac{P_a^0}{P_a^0 - P_w^0} = \frac{Q_1}{Q_0}\frac{P_a^0}{P_a^0 - P_w^0},$$

where Q_0 is the summation of the flow rates to the main and side branches. For equations (E3) and (E5), we define two coefficients $w = 1/C_3 = P_a^0 / \left(P_a^0 - P_w^0\right) = P_a / \left(P_a - P_w\right)$ and $k=Q_1/Q_0$. Therefore, we finally obtain the equations of

(E6) $$\Delta FFR'_p = \frac{\Delta FFR_p}{1 - kw \times \Delta FFR_d},$$

and

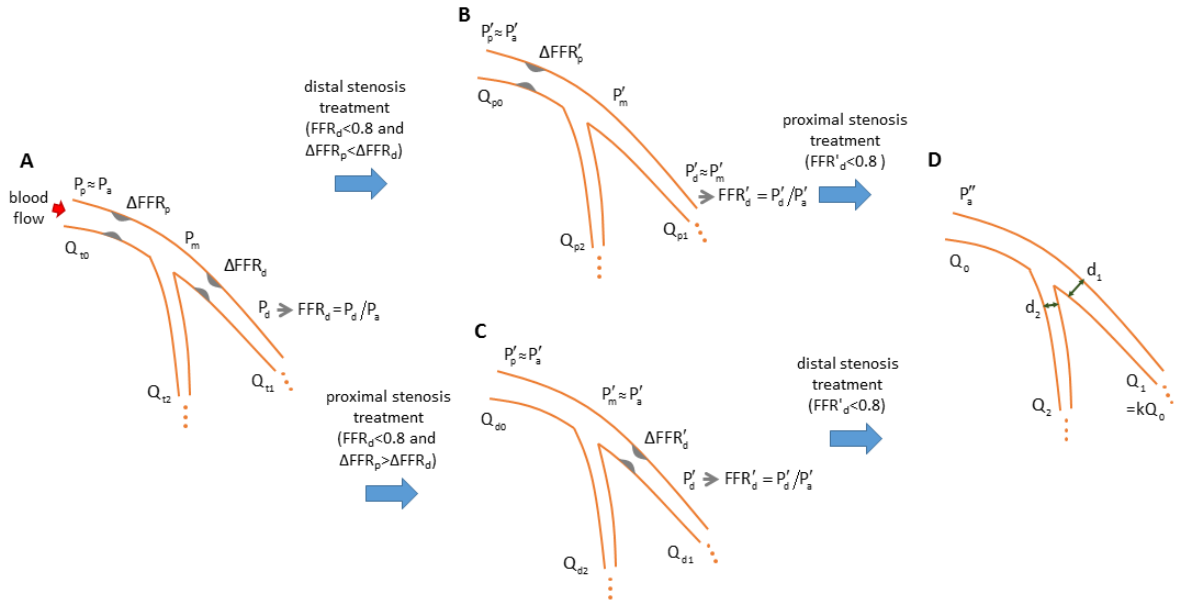
(E7) $$\Delta FFR'_d = \frac{\Delta FFR_d}{1 - w \times \Delta FFR_p}.$$

E. Estimation of flow fraction to distal main branch (k)

The prediction of $\Delta FFR'_{p,pred}$ required knowing the flow rate to each coronary branch, which is not a diagnostic measure. However, k could be estimated with the allometric scaling law of flow bifurcation using the diameters of coronary branches [4], as follows:

$$k = Q_1/(Q_1 + Q_2) = d_1^3/(d_1^3 + d_2^3),$$

where Q_1 and Q_2 represent the flow rates to the distal main and side branches, respectively (**Online Figure 1D**), and d_1 and d_2 represent the diameters of the distal main and side branches in normal segments, respectively.

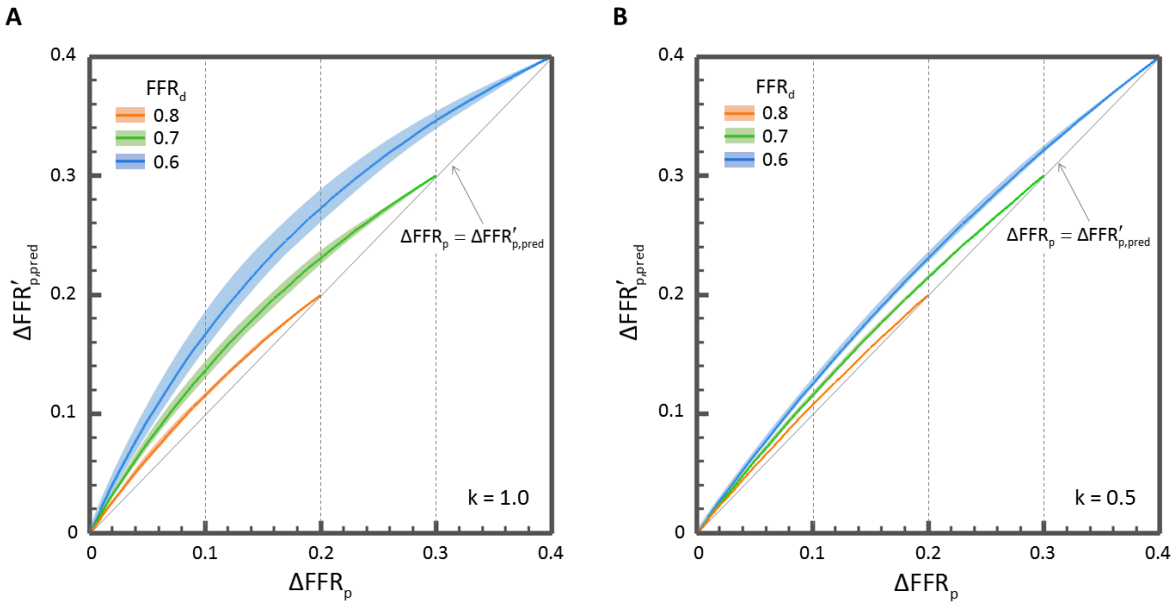


Online Figure 1. Haemodynamic assessments for stenting coronary tandem lesions. A) The FFR gradients over proximal and distal stenoses are calculated as $\Delta FFR_p = FFR_p - FFR_m$ and $\Delta FFR_d = FFR_m - FFR_d$, respectively. B) After the treatment of a distal stenosis, the FFR gradient over the remaining proximal stenosis becomes $\Delta FFR'_p$. C) After the treatment of a proximal stenosis, the FFR gradient over the remaining distal stenosis becomes $\Delta FFR'_d$. D) Haemodynamic status following treatment of the remaining stenosis. The coronary flow rate (Q) of each branch is denoted by subscripts according to location (0, ostium; 1, main branch; 2, side branch) and lesion (t, tandem; p, proximal; d, distal). d_1 and d_2 are the diameters of the main and side branches, respectively.

FFR: fractional flow reserve; P_a: mean aortic pressure; P_p, P_m, and P_d: mean coronary pressures at positions proximal to the tandem lesion, between stenoses, and distal to the tandem lesion, respectively; FFR_p, FFR_m, and FFR_d: FFR values defined at the locations corresponding to P_p, P_m, and P_d, respectively; ′: after treatment of a stenosis; ′′: after treatment of both proximal and distal stenoses

F. Estimation of wedge pressure (P_w)

The wedge pressure (P_w) measurement necessary for the calculation of $\Delta FFR'_{p,pred}$ and $\Delta FFR'_{d,pred}$, has been considered as the main obstacle preventing the practical use of prediction models [5,6]. In the present study, P_w/P_a was assumed to be 0.25 [5,7], correspondingly w=1.33. To quantify the uncertainty associated with P_w, variations in $\Delta FFR'_{p,pred}$ were investigated based on the published standard deviation (SD) (P_w/P_a=0.25±0.10) [5,8] (**Online Figure 2**). When both the proximal and distal stenoses reached the criterion of a percutaneous coronary intervention (PCI) ($\Delta FFR_p=\Delta FFR_d$=0.2), the estimated error of the predicted FFR was <0.02. Initial data from four patients also had an error of <0.01 between the FFR values predicted with P_w/P_a=0.25 and the measured wedge pressure.



Online Figure 2. Uncertainty of $\Delta FFR'_{p,pred}$ associated with the wedge pressure for $FFR_d=1-\Delta FFR_p-\Delta FFR_d$ =0.6, 0.7 and 0.8. Coloured solid line denotes $w=P_w/P_a$=0.25 and the shaded region indicates the variations in $\Delta FFR'_{p,pred}$ whose upper and low boundaries

correspond to w=0.35 and 0.15. A) Negligible side branch (k=1). B) Large side branch (k=0.5). With a negligible side branch (k=1.0), the maximum discrepancy was −0.013–0.019 (ΔFFR_p=0.12, and ΔFFR_d=0.28), while with a large side branch (k=0.5), the maximal discrepancy was −0.004–0.006 (ΔFFR_p=0.14, and ΔFFR_d=0.26).

FFR: fractional flow reserve; ΔFFR_p and ΔFFR_d: FFR gradients over proximal and distal stenoses, respectivley; P_w: mean wedge pressure; P_a: mean aortic pressure; k: flow fraction of main branch at bifurcation point of interest; ′: after treatment of a stenosis; pred: predicted

G. Equivalence with the conventional model for tandem lesion without side branch

When the side branch flow is negligible, k becomes almost 1. To examine the equivalence, we express the equations (E6) and (E7) in the same manner as the conventional model in which a side branch was not taken into account [3].

When k is ~1, after stenting the distal stenosis, FFR for the remaining stenosis is

$$FFR'_{d,pred} = 1 - \Delta FFR'_{p,pred} = 1 - \frac{\Delta FFR_p}{1 - w \times \Delta FFR_d}.$$

By using the substitutions $\Delta FFR_p=(P_a-P_m)/P_a$, $\Delta FFR_d=(P_m-P_d)/P_a$ and $w=P_a/(P_a-P_w)$, it becomes

$$FFR'_{d,pred} = 1 - \frac{\frac{P_a - P_m}{P_a}}{1 - \frac{P_a}{P_a - P_w}\frac{P_m - P_d}{P_a}} = 1 - \frac{(P_a - P_w)(P_a - P_m)}{P_a(P_a - P_m + P_d - P_w)} = \frac{P_d - (P_m/P_a)P_w}{(P_a - P_m + P_d - P_w)}.$$

On the other hand, after stenting the proximal stenosis, FFR for the remaining stenosis is

$$FFR'_{d,pred} = 1 - \Delta FFR'_{d,pred} = 1 - \frac{\Delta FFR_d}{1 - w \times \Delta FFR_p}.$$

Likewise,

$$FFR'_{d,pred} = 1 - \frac{\frac{P_m - P_d}{P_a}}{1 - \frac{P_a}{P_a - P_w}\frac{P_a - P_m}{P_a}} = 1 - \frac{(P_a - P_w)(P_m - P_d)}{P_a(P_m - P_w)}.$$

Consequently, both the equations for $FFR'_{d,pred}$ are the same as those in the conventional model [3]. Note that this equivalence is valid only in the limited cases with FFR_p=1 and k=1 (no side branch).

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INVITED EXPERT'S FINAL COMMENTS

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I have read with interest the long reply/resubmission by Dr Kweon and Dr Young-Hak Kim with respect to this complex issue.

Although I appreciate the extensive work done by these authors and the extensive way they have tried to answer and argue my earlier comments, I still believe that their answers are only very partially correct and that the conjectural assumptions made in their original paper are still present.

More in general, one can argue about several of these issues but personally I believe that the complete theoretical set-up is unnecessarily complex and thereby not contributing to our knowledge and understanding of coronary physiology.

Below I explain my specific comments and give my answers to the authors in more detail:

1. I believe that the assumption that microvascular resistance (R_{min}) increases as distal pressure (P_d) falls is a misunderstanding and I believe that sufficient studies have been performed in both animals and humans to show that. For more details I refer to an experimental study by Fearon et al [1], and a study in humans by Aarnoudse et al [2]. In the meantime, Spaan et al admitted that their initial assumption was not true because they neglected coronary wedge pressure (presentations at TCT 2016).
2. My questions about the meaning of the resistances R1 and R2 have not yet been satisfactorily answered.
3. The issue of assuming that P_w is equal to 25 mmHg and equal to side branch and main branch: one can argue how valid this is. Anyway, it is not in congruence with clinical observations and I believe that if a mathematical model claims to be as complex as the present one, P_w should be taken into account as it is and not be replaced by a default value. In addition, in clinical practice it is quite simple to measure P_w.
4. Comment 4 about the shortcomings of QCA: here also one can wonder why it is necessary to introduce uncertainties in a theoretical framework if that is not mandatory and if a simpler framework is available.
5. Boundary values: despite the defence of the authors that their model would be valid in boundary conditions, this is not completely the case.

In the meantime, this initial paper, the letters to the editors, the comments of the different

experts, the replies and all the other discussions are leading to a huge volume of correspondence. I wonder if it is useful and feasible to continue with these discussions as I fundamentally believe that – due to the intrinsic shortcomings of this theoretical model – there will remain different opinions between the authors themselves and the authors of the letters and consulted experts.

I fully understand the dilemma for the editors of EuroIntervention as to how to continue with the issue and what to publish about it.

My personal feeling is that a notice should be made in one of the upcoming issues of EuroIntervention that the content of the published paper was disputed seriously by several readers and consulted experts but that the details are too complex and too sophisticated to contribute to the general field of interventional cardiology and are beyond the scope of EuroIntervention, and that the complete set of correspondences is available for interested readers.

References

1. Fearon WF, Aarnoudse W, Pijls NH, De Bruyne B, Balsam LB, Cooke DT, Robbins RC, Fitzgerald PJ, Yeung AC, Yock PG. Microvascular resistance is not influenced by epicardial coronary artery stenosis severity: experimental validation. Circulation. 2004;109:2269-72.
2. Aarnoudse W, Fearon WF, Manoharan G, Geven M, van de Vosse F, Rutten M, De Bruyne B, Pijls NH. Epicardial stenosis severity does not affect minimal microcirculatory resistance. Circulation. 2004;110:2137-42.