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BASIC SCIENCE

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Respiration-related variations in Pd/Pa ratio and fractional flow reserve in resting conditions and during intravenous adenosine administration

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Abstract

Aims: We evaluated the occurrence and physiology of respiration-related beat-to-beat variations in resting Pd/Pa and FFR during intravenous adenosine administration, and its impact on clinical decision-making.

Methods and Results: Coronary pressure tracings in rest and at plateau hyperemia were analyzed in a total of 39 stenosis from 37 patients, and respiratory rate was calculated with ECG-derived respiration (EDR) in 26 stenoses from 26 patients. Beat-to-beat variations in FFR occurred in a cyclical fashion and were strongly correlated with respiratory rate ($R^2 = 0.757$, $p < 0.001$). There was no correlation between respiratory rate and variations in resting Pd/Pa. When single-beat averages were used to calculate FFR, mean ΔFFR was 0.04 ± 0.02. With averaging of FFR over three or five cardiac cycles, mean ΔFFR decreased to 0.02 ± 0.02, and 0.01 ± 0.01, respectively. Using a FFR ≤ 0.80 threshold, stenosis classification changed in 20.5% (8/39), 12.8% (5/39) and 5.1% (2/39) for single-beat, three-beat and five-beat averaged FFR. The impact of respiration was more pronounced in patients with pulmonary disease (ΔFFR 0.05 ± 0.02 vs 0.03 ± 0.02, $p = 0.021$).

Conclusion: Beat-to-beat variations in FFR during plateau hyperemia related to respiration are common, of clinically relevant magnitude, and frequently lead FFR to cross treatment thresholds. A five-beat averaged FFR, overcomes clinically relevant impact of FFR variation.

KEYWORDS
clinical research, fractional flow reserve, stable angina

Abbreviations: ADVISE II, ADenosine Vasodilator Independent Stenosis Evaluation II study; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; EDR, electrocardiogram-derived respiration; FFR, fractional flow reserve; Pa, aortic pressure; Pd, distal coronary pressure; Pd/Pa, distal coronary to aortic pressure ratio; Pv, venous pressure.

1 | INTRODUCTION

In patients with ischaemic heart disease, physiology-guided coronary revascularisation improves clinical outcomes compared to revascularization guided by coronary angiography alone. This is attributed to the fact that angiography alone is not able to identify the functional severity of a coronary artery stenosis. The most widely applied physiological measurement to identify functional stenosis severity is the fractional flow reserve (FFR), which has been validated in large randomized clinical trials and is supported by international guidelines.[1] FFR is defined as the ratio of mean coronary pressure distal to the stenosis (Pd), to mean aortic pressure (Pa) during maximal hyperaemia; a state in which coronary pressure measurements can theoretically be used as an estimate of stenosis-induced coronary flow impairment.[2] This state of maximal hyperaemia is therefore critical for the concept of FFR and is achieved by the administration of pharmacological vasodilators, such as adenosine, which can be administered either as an intracoronary bolus or by continuous intravenous infusion. Although more cumbersome in practice, intravenous infusion of adenosine has been advocated in best-practice guidelines, and was the dominant route of vasodilator administration applied in the randomized FFR studies.[3,4] Intravenous adenosine provides a plateau hyperaemic state, allowing assessment of FFR as well as conditions to perform an FFR pullback curve. However, it has been noted that there is distinct instability of FFR particularly during this plateau hyperaemic state. Different haemodynamic response patterns have been described,[5,6] but also more common beat-to-beat variations have been identified. These hemodynamic patterns have been ascribed to variability in the systemic blood pressure and heart rate response to adenosine infusion, but beat-to-beat variations have been poorly described. When adenosine is administered intravenously, it first passes through the pulmonary vasculature before reaching the coronary vasculature, inducing unfavorable respiratory side effects, such as increased respiratory activity.[7–9] Robust assessment of the influence of adenosine-induced increased respiratory activity and the magnitude of its impact on FFR is lacking. Therefore, this study aimed to identify the influence of respiration on intracoronary pressures during resting conditions and continuous intravenous infusion of adenosine and to assess its effect on clinical decision making by means of FFR.

2 | METHODS

2.1 | Study design

Patients enrolled in the ADVISE II (ADenosine Vasodilator Independent Stenosis Evaluation II) study at the Academic Medical Centre (Amsterdam, The Netherlands) were included in this post-hoc analysis. The ADVISE II study involved patients with stable coronary artery disease eligible for coronary angiography and physiological assessment of coronary stenosis severity by means of FFR. Exclusion criteria were restricted to culprit vessels of acute coronary syndromes, serial stenosis, left main stenosis, significant valvular pathology, prior coronary artery bypass graft surgery, patients with severe asthma or COPD who were deemed unfit for adenosine infusion by the clinician and other absolute contraindications for adenosine administration (heart rate<50 beats/min, and systolic blood pressure<90 mm Hg).[10] Definitions used are conform definitions used in the ADVISE II study. The institutional ethics committee approved the study procedures, and all patients gave written informed consent.

2.2 | Procedure and data acquisition

After diagnostic angiography, a 0.014″ pressure-sensor-equipped guide wire (PrimeWire Prestige Plus, Volcano Corporation, Rancho Cordova, CA) was passed into the target vessel distal to the target stenosis to measure distal coronary pressure (Pd). Aortic pressure (Pa) was measured through the guiding catheter. Nitroglycerine (0.2 mg) was administered intracoronary prior to physiological measurements in all patients. Pressure recordings were made at baseline for at least 20 s before starting intravenous infusion of adenosine and throughout intravenous infusion of adenosine at a rate of 140 μg/kg per minute administered via a femoral venous sheath or through a venous cannula in a large antebrachial vein, and maintained for at least 2 min. Surface ECG and all hemodynamic data was recorded on a dedicated console (*s5i* Imaging System console, Volcano Corporation, Rancho Cordova, CA).

2.3 | Haemodynamic signal analysis

The haemodynamic data were analyzed offline using custom software written in Matlab (Mathworks, Inc, Natick, MA). Beat-to-beat averages were determined for Pa, Pd, and the Pd/Pa ratio during both resting conditions and during stable hyperaemia. Baseline and stable hyperaemia were identified by visual inspection of the hemodynamic trace. The baseline sample was defined as beginning of the recording up until start adenosine infusion which was identified by a bookmark according to the study protocol. A baseline sample of at least 20 s was available as mandated by the protocol. Stable hyperaemia was defined as the period of the recording in which no systematic alterations occurred after start of adenosine infusion, which lasted at least 2 min in total as mandated by the study protocol. The contribution of the systolic and diastolic components to respiratory variation in the samples was calculated after decomposing the data into a systolic and a diastolic pressure signal by defining the R-wave on the ECG recorded by the console as the beginning of systole and the dicrotic notch as the beginning diastole. The dicrotic notch was derived from the first derivative of the Pa blood pressure trace as the first moment of deceleration following the peak acceleration. Sample periods were taken from the traces for a length of at least three successive respiratory cycles where ECG and pressure signal quality was optimal. A mean value was calculated for each of these signals, as well as the absolute and relative delta calculated from the difference between

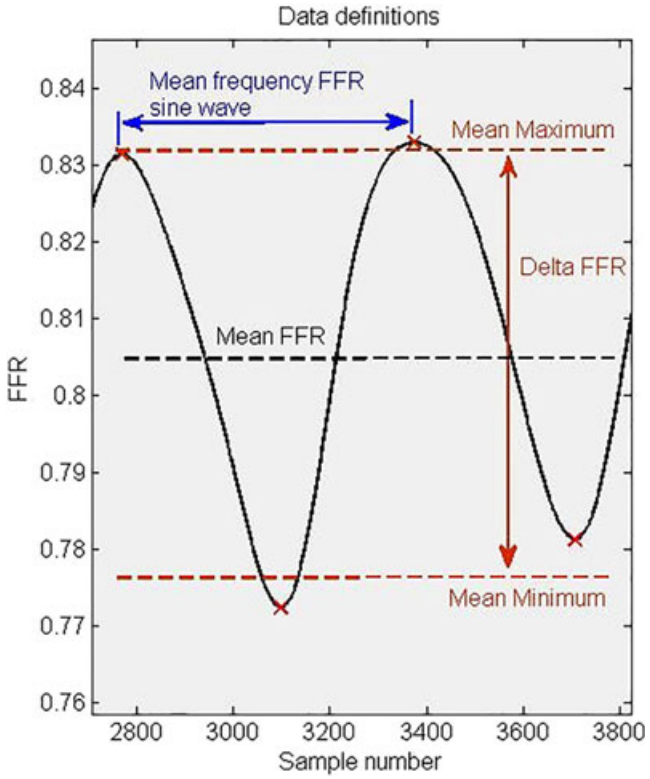

FIGURE 1 Definitions of data used for analysis [Color figure can be viewed at wileyonlinelibrary.com]

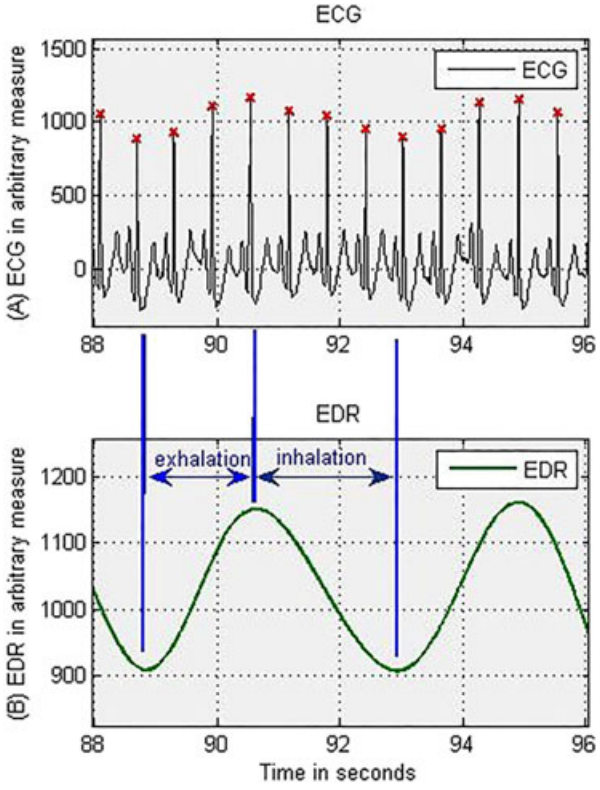

FIGURE 2 ECG-derived respiration (EDR). Inhalation causes the impedance across lung tissue to increase causing the amplitude of the R-peak on the ECG to decrease. These fluctuations are utilized to compile an EDR-signal [Color figure can be viewed at wileyonlinelibrary.com]

the mean highest and mean lowest measured values occurring in a sinusoid manner (Figure 1).

2.4 | ECG-derived respiration

A respiratory signal was derived from the ECG signal, for which a signal was composed from the fluctuations in the R-wave amplitude in the ECG signal due to motion of the thorax caused by respiration (Figure 2). Respiration-associated motion of the thorax effectively results in a change in impedance and movement of the apex of the heart.[11] An EDR signal was composed by interpolating though the R-wave amplitudes in the ECG-signal, as described previously in detail.[12] From the EDR signal, mean respiratory rate and an estimation of depth were measured throughout the entire physiological recording by respectively calculating the average sample length between EDR-peaks and the average delta of the EDR-signal, both during resting conditions and throughout the adenosine infusion.

2.5 | Statistical analysis

Data was analyzed on a per-patient basis for clinical characteristics, and on a per-vessel basis for all other calculations. Normality and homogeneity of variances were tested using Shapiro–Wilk and Levene tests. Continuous variables are presented as mean ± SD or median (first, third quartile [Q1, Q3]), and were compared with Student *t* test or Mann–Whitney U test, as appropriate. Categorical variables are presented as counts and percentages, and were compared using Fisher exact test. After visual evaluation of the EDR signal and the FFR signal, we first assessed whether the frequency of cyclic variation in FFR (Figure 1) was related to the EDR-derived respiration frequency. The factors associated with respiration-related cyclic variation in FFR were further assessed using two regression models. First, univariate regression was performed to identify all variables (including all baseline characteristics) associated with the variation in FFR during stable hyperaemia. Subsequently, multivariate regression analysis was performed which included all variables associated with FFR-variation in univariate analysis ($p < 0.1$). All statistical analyses were performed using the SPSS version 20 (IBM Corp., Armonk, NY, USA). $p < 0.05$ was considered statistically significant.

3 | RESULTS

A total of 48 stenoses from 46 patients were included. Of these, nine stenoses were excluded by the ADVISE II core laboratory on the basis of artifacts precluding data analysis, such as pressure drift and

pressure damping, and 11 patients were excluded from analysis with EDR derived variables due to ECG traces of insufficient quality for EDR analysis. Consequently, the study population comprised 39 stenoses from 37 patients, and the EDR cohort comprised 26 stenoses from 26 patients. Mean age of the study population was 63.2 ± 9.5 years, and 62.2% of patients were male. Mean angiographic stenosis severity was 54.2 ± 9.4%, and mean FFR was 0.84 ± 0.07. Complete baseline clinical and angiographic characteristics are documented in Tables 1 and 2.

3.1 | Relationship of EDR and coronary pressure measurements

For the whole study population, heart rate was 83.3 ± 12.6 beats/min, and respiratory rate was 17.1 ± 2.3 in resting conditions, and 17.5 ± 1.8 during hyperaemia ($p = 0.466$). In the EDR cohort, delta-EDR as a measure of depth of breathing was 119.8 ± 52.5 (in arbitrary units) during baseline and increased to 179.1 ± 117.7 during hyperaemia ($p = 0.007$).

TABLE 2 General characteristics of coronary stenosis included in study ($N = 39$)

	Mean ± SD or *N* (%)
Vessels	39
Left anterior descending artery	23 (59.0)
Left circumflex	6 (15.4)
Right coronary artery	10 (25.6)
Stenosis characteristics	
Lesion length (mm)	10.6 ± 6.4
Reference vessel diameter (mm)	2.7 ± 0.8
Percentage diameter stenosis	54.2 ± 9.4
FFR	0.84 ± 0.07
Lesion type (AHA)	
A	18 (46.2)
B1/B2	17 (43.6)
C	4 (10.3)
Current in-stent restenosis	0 (0)

Abbreviations: AHA, American Heart Association; FFR, fractional flow reserve.

TABLE 1 Baseline characteristics of patients included in study ($N = 37$)

	Mean ± SD or *N* (%)		Mean ± SD or *N* (%)
Baseline characteristics		Renal dysfunction (serum creatinine >2.0)	0 (0)
Patients	37	Previous myocardial infarction	13 (35.1)
Age, yrs	63.2 ± 9.5	Previous PCI	15 (40.5)
Sex, %male	23 (62,2)	Previous CABG	1 (2.7)
Mean baseline systolic blood pressure, mmHg	136.5 ± 27.7	Renal dysfunction (serum creatinine >2.0)	0 (0)
Mean baseline diastolic blood pressure, mmHg	73.6 ± 11.6	Previous myocardial infarction	13 (35.1)
Mean baseline heart rate, beats/min	69.4 ± 9.8	***Clinical presentation***	
BMI	28.1 ± 4.0	Stable angina	22 (59.5)
HR baseline, beats/min	69.3 ± 9.7	Unstable angina	6 (16.2)
HR, beats/min	83.5 ± 12.7	NSTEMI (>48 h before enrolment)	6 (16.2)
EDR-RR baseline, cycles/min	17.1 ± 2.3	STEMI (>48 h before enrolment)	1 (2.7)
EDR-RR hyperaemia, cycled/min	17.5 ± 1.8	Other	2 (5.4)
Medical history		**Medication**	
Pulmonary disease	8 (21.6)	Aspirin	33 (89.2)
Valvular disease	0 (0)	Beta Blocker	32 (86.4)
Reduced ejection fraction (<30%)	0 (0)	Statins	30 (81.1)
Hypertension	22 (59.4)	ACE inhibitor	20 (54.1)
Diabetes mellitus	9 (24.3)	Clopidogrel	6 (16.2)
(previous) smoker	12 (32.4)	Prasugrel	2 (5.4)
Family history	18 (48.6)	Nitrates	19 (51.4)
		Ticagrelor	10 (27.0)

Abbreviations: CABG, coronary artery bypass graft; EDR-RR, electrocardiography derived respiration-respiratory rate; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

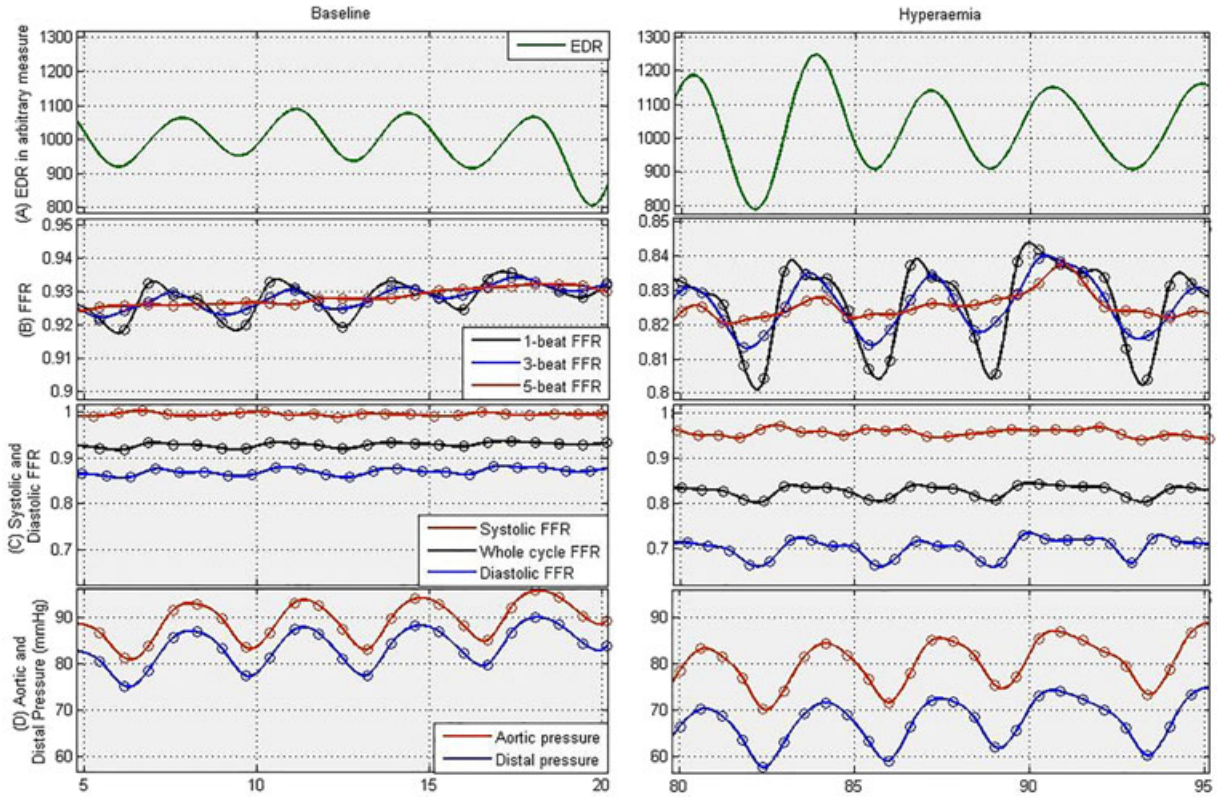

FIGURE 3 Example of respiratory variations in various indices. Left panel depicts resting conditions and right panel hyperaemia. (A) EDR-signal (green) in both resting condition (left panel) and during intravenous infusion of adenosine at a rate of 140 μg/kg per minute (right panel). (B) Clinical impact of respiratory variations in single-beat FFR (black), three-beat averaged FFR (blue) and five-beat averaged FFR (red). (C) Respiratory variations in a single-beat FFR (black) decomposed into a systolic (red) and a diastolic (blue) component and the effect of adenosine infusion on these values. (D) Respiratory variations in Pd (blue) and Pa (red) and the effect of adenosine infusion on these values (right panel) [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | Relationship between respiration and coronary hemodynamics

As illustrated in Figure 3, there was a striking similarity between the respiration and the cyclic variations in FFR. Concordantly, the frequency of cyclic beat-to-beat variations in FFR were strongly correlated to the respiratory rate, whereas no correlation was documented between the frequency of cyclic variations in Pd/Pa and respiratory rate (Resting conditions (Pd/Pa): $R^2 = 0.158$, $p = 0.201$; Hyperaemia (FFR): $R^2 = 0.757$, $p < 0.001$; Figure 3).

In resting conditions, when using single-beat averages to calculate Pd/Pa, mean ΔPd/Pa amounted to 0.01 ± 0.00, and was similarly neglectable when averaging over 3-beats (0.01. ±0.00). Even when single-beat averages were used to calculate Pd/Pa, none of the patients showed significant cyclic variation in Pd/Pa.

When single-beat averages were used to calculate FFR during adenosine-induced hyperaemia, mean ΔFFR amounted to 0.04 ± 0.02. In total, 20.5% (8/39) of stenosis and 21.6% (8/37) patients showed a ΔFFR > 0.05 during stable hyperaemia. For three-beat averaged FFR, mean ΔFFR amounted to 0.02 ± 0.01, and 5.1% (2/39) of stenosis showed a ΔFFR > 0.05 associated with the respiratory cycle. Using five-beat averaging of FFR, mean ΔFFR amounted to 0.01 ± 0.01 and led to the absence variation in FFR > 0.05. The effect of beat averaging on FFR is illustrated in Figure 4. Using a ≤ 0.80 FFR treatment threshold, stenosis classification changed in 20.5% (8/39), 12.8% (5/39) and 5.1% (2/39) of cases on the basis of a single-beat, three-beat and five-beat averaged FFR, respectively, during plateau hyperaemia. When the FFR treatment threshold of <0.75 was used, the proportion of patients in whom classification changed with a single-beat averaged FFR was 17.9% (7/39), which decreased to 5.1% (2/39) and 2.6% (1/39) for three-beat and five-beat averaged FFR, respectively. Furthermore, based on a single-beat FFR 2.6% (1/39) of FFR crossed the gray zone completely and was < 0.75 at its minimum and > 0.80 at its maximum. The impact of using per-beat averages of FFR versus three-beat or five-beat averages is illustrated in Figure 3.

3.3 | Origin of respiration-related variation in FFR

As illustrated in Figure 3, the cyclic variation in FFR dominantly originated from changes in the diastolic portion of FFR. The variation of systolic FFR during hyperaemia was 0.029 ± 0.017, and the variation in diastolic FFR was 0.06 ± 0.04 ($p < 0.001$). ΔPa amounted to 6.11 ± 4.17 mmHg and did not differ significantly from ΔPd, which

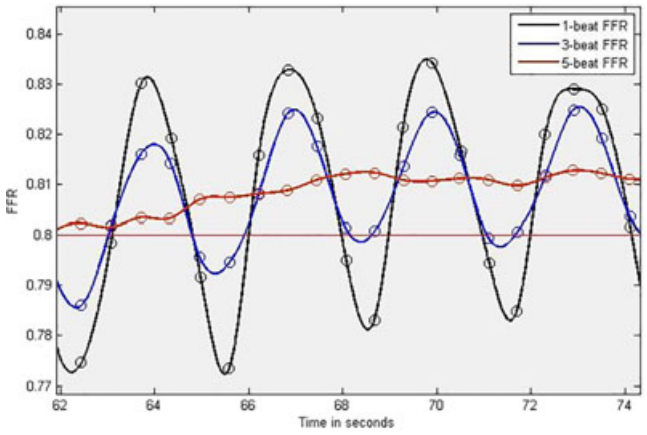

FIGURE 4 Clinical impact of per-beat average FFR. The single-beat FFR (black) and three-beat averaged FFR (blue) vary across the treatment threshold (red vertical line; 0.80) during the respiratory cycle and their lowest measured value occur under the treatment threshold. In contrast, the five-beat averaged FFR (red) provides a more stable signal and all measured values occur above the treatment threshold [Color figure can be viewed at wileyonlinelibrary.com]

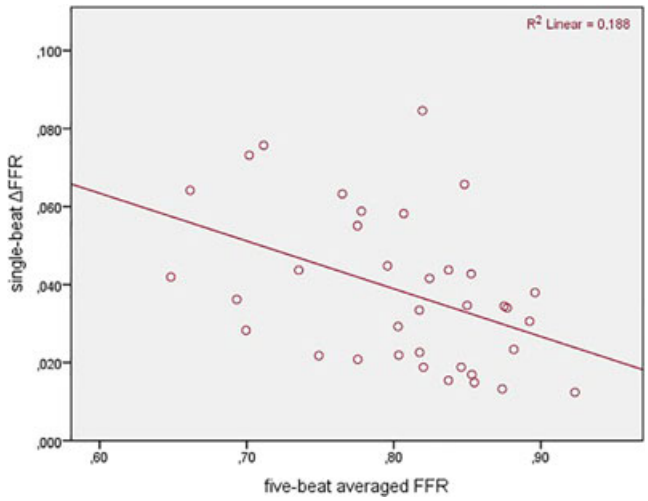

FIGURE 5 Scatterplot of SMFFR-value and ΔFFR with regression line. Regression analysis found a significant correlation between the SMFFR-value and ΔFFR ($R^2 = 0.188$, $p = 0.008$). Increased SMFFR-value results in increased ΔFFR. SMFFR: smart minimum fractional flow reserve (5-beat averaged FFR) [Color figure can be viewed at wileyonlinelibrary.com]

amounted to 6.45 ± 4.27 mmHg ($p = 0.078$). Furthermore, single-beat ΔFFR was significantly correlated to the five-beat averaged FFR-value ($R^2 = 0.188$, $p = 0.008$), as illustrated in Figure 5.

3.4 | Association between clinical and procedural characteristics and cyclic FFR variations

In univariate analysis, a history of (mild) pulmonary disease and a history smoking were the only clinical or procedural characteristics associated with the respiration-related ΔFFR during hyperaemia. In multivariate analysis, only pulmonary disease was documented to be independently associated with the respiration-related ΔFFR. The ΔFFR was significantly higher in patients with reported pulmonary disease (0.05 ± 0.02 in patients with pulmonary disease versus 0.03 ± 0.02 in patients without pulmonary disease ($p = 0.021$). Respiration-related variation in FFR was notably not related to angiographic stenosis characteristics.

4 | DISCUSSION

This is the first study to quantify respiration-associated beat-to-beat variations of Pd/Pa in resting conditions and FFR during plateau hyperaemia induced by the intravenous infusion of adenosine. The main finding of this study is that, where no relevant effect of respiration is noted on Pd/Pa in resting conditions, FFR during plateau hyperaemia induced by intravenous adenosine administration varies significantly throughout the respiratory cycle. Almost 21% of stenosis changed classification on the basis of this variation. The clinical impact of such FFR variation critically depends on the amount of heart cycles averaged to calculate FFR. Mean ΔFFR decreased from 0.04 to 0.02 to 0.01 when averaged over one heart cycle, three heart cycles, or five heart cycles, respectively. Given the magnitude of such FFR-variation, the identification of this respiration-related FFR variation is relevant for clinical practice. Not accounting for these respiratory variations could lead to inaccurate assessment, especially during FFR-pullback recording of diffuse disease or sequential lesions.

4.1 | Contemporary practice versus standardization guidelines

Standardization papers for assessment of coronary physiology advocate a uniform approach in acquiring and interpreting data.[13] However, these guidelines do not provide guidance on averaging of FFR across multiple heart beats. Software on commercially available FFR-systems default to measuring FFR as the lowest value averaged over one heart cycle. When using intravenous adenosine infusion to induce hyperaemia, such an approach is prone to uncertainty at least partly on the basis of respiratory variation of FFR, as documented in the present study. This becomes most relevant when manual re-allocation of the measurement timing is performed, or when pressure wire pullback recording is required. To overcome such influence of beat-to-beat variations in the FFR-value, others have suggested a three-beat average to identify FFR.[14] Our current results suggest that this might not be sufficient especially when respiratory variations are more pronounced, as can be expected in patients with (mild) pulmonary disease. Since these fluctuations are due to hemodynamic changes related to the respiratory cycle, as discussed below, the number of cardiac cycles required to optimally average FFR is the number of heart beats that occur during one respiratory cycle. For this study population, heart rate was 83.3 ± 12.6 beats/min and respiratory rate

17.5 ± 1.8 inhalations/min, which amounts to a ratio of heart rate to respiratory rate of 4.8. Therefore, we suggest using a five-beat averaged FFR to minimize the effect of respiration on FFR measurements, was proposed in an automated algorithm for the detection of the minimal Pd/Pa ratio, smart minimum FFR.[6] In the present study, a five-beat average for the calculation of FFR had distinct advantages to overcome influence of beat-to-beat FFR variation.

4.2 | Physiology of respiration-associated variations in coronary hemodynamics

Beat-to-beat variations in FFR occur in a cyclical fashion corresponding to the motion of the thorax during respiration. Since FFR corresponds to the ratio of distal coronary to aortic pressure, alterations in FFR throughout the respiratory cycle can only occur if the hemodynamic effects of in- and exhalation have a different impact on aortic and distal coronary pressure. This is likely explained by the fact that, in absolute terms, external pressures will affect aortic and distal coronary pressure to the same extent. In the presence of a coronary stenosis, where distal coronary pressure is reduced relative to the aortic pressure, changes in external pressures will have a proportionally greater effect on distal coronary pressure. Therefore, any alteration in external pressure that influences aortic and distal coronary pressure may lead to variation of FFR. This also illustrates that the impact of external pressures will become greater when the difference between distal coronary pressure and aortic pressure becomes larger. This is supported by the fact that a decrease in the absolute five-beat averaged FFR-value was strongly related to an increase in FFR variation in the present study. Similarly, such external pressures have a proportionally greater influence during cardiac diastole than during systole. Accordingly, we documented that the variation of the diastolic portion of the FFR trace is larger than the variation in the systolic portion.

The most evident external pressure that varies with respiration is the direct transmural pressure originating from fluctuations in intrathoracic pressure due to respiration. During inhalation, intrathoracic pressure decreases, leading to a relative decrease in external compressive forces. In contrast, during exhalation, intrathoracic pressure increases, leading to a relative increase in external compressive forces. Due to the different effect of such external compressive forces on distal coronary pressure and aortic pressure, FFR tends to decrease (become more abnormal) during inhalation, and to increase (become more normal) during exhalation, as is supported by the findings in the present study (Figure 5). Another factor that could have a greater effect on distal coronary pressure compared to aortic pressure is central venous pressure (Pv), for which a correction was included in the original FFR equation (FFR = (Pd-Pv)/(Pa-Pv)).[15] Venous pressure, which usually ranges between 5 and 10 mmHg, is assumed to be negligible in comparison to the mean aortic pressure and to hold no clinical significance for the calculation of FFR when elevated right atrial pressures are not expected. However, venous return changes throughout the respiratory cycle and hence also right atrial pressure. Right atrial pressure and its effects on the stenosis pressure gradient therefore change throughout the respiratory cycle, and it cannot be excluded that cyclic changes in venous pressure are associated with FFR variation.

4.3 | Resting conditions versus hyperaemia

Our results indicate that respiration does not influence the distal coronary to aortic pressure ratio in resting conditions, but only impacts this ratio (FFR) during intravenous adenosine administration. This may occur from the fact that besides the typical side effect of chest discomfort, hypotension and flushing, adenosine has respiratory side effects in the form of dyspnoea and an urge to breathe deeply.[9] In young healthy subjects, intravenously infused adenosine has a dose dependent respiratory stimulatory effect: increasing minute volume, tidal volume, and thoracic excursion.[7,8] Hence, the respiratory effects of intravenously infused adenosine may aggravate the impact related to intrathoracic pressure changes described above. This also supports the finding that FFR variations are larger in patients with documented pulmonary disease whom may be more prone to adenosine-induced respiratory stimulation. Intracoronary administration of adenosine overcomes such side effects and allows for spot measurement of FFR only due to the short duration of the hyperaemic plateau phase. In addition, other endothelium-independent vasodilators such as nicorandil or papaverine are available to induce a hyperaemic plateau phase to allow measurement of FFR and the performance of pressure pullback curves. Nonetheless, the presence or absence of respiration-related FFR variations at maximal hyperaemia using these alternative agents has not been documented.

5 | LIMITATIONS

The quality of the EDR-signal is affected by instabilities in the ECG signal due to movement of or talking by the patient, as well as technical artifacts, arrhythmias, heart rate variability, regular ventricular extra systole or patient movements such as a cough. This is indeed important since the current analysis was performed retrospectively. As such, the ECG data has not been recorded for this purpose, which led a significant number of ECG traces to be unsuitable for EDR analysis. The ECG signal was derived from the device console, which had the advantage of providing ECG data acquired simultaneously with the pressure waveforms. However, higher quality EDR signals can be obtained from high sampling frequency ECG, which allows more sophisticated EDR techniques to be used. For the current manuscript, next to the ADVISE II core laboratory assessment of the physiological traces, elaborative evaluation of the ECG traces was performed to ensure absence of factors influencing EDR-derived measures. Moreover, the number of cases included in the analysis is limited, and it cannot be excluded that independent predictors FFR variation during stable

hyperaemia were not identified due to a lack of statistical power. Furthermore, respiratory variation in left ventricular end-diastolic pressure have been reported and may provide more insight into the physiology of respiration-related variations in FFR.[16] However, these data were not available in the ADVISE II study, and should be part of further prospective studies.

6 | CONCLUSION

When FFR is measured during hyperaemia induced by intravenous adenosine administration, beat-to-beat variations in FFR occur with the respiratory cycle. These respiration-associated variations can cause FFR measurements to cross treatment thresholds, and thereby influence clinical decision-making, especially when manual re-allocation of the measurement timing is performed, or when pressure wire pull-back recording is required. To overcome such influence of beat-to-beat variations in the FFR-value, five-beat averaged FFR algorithms are preferred. Their application, however, requires operator awareness, particularly during pressure wire pullback maneuvers under hyperaemic conditions.

Impact on daily practice

The present study documents the clinical relevance of beat-to-beat FFR variations, and suggests that its effects can be minimized by the use of five-beat averaged FFR algorithms. Such may be changing the averaging options in commercially available FFR consoles, or applying the recently introduced smart minimum FFR algorithm which includes five-beat averaging of FFR. The application of such algorithms, however, requires operator awareness as such averaging influences pressure wire pullback technique. Pullback maneuvers should be much slower to allow for averaging in order to obtain accurate measurements, thereby becoming more cumbersome to perform. Nonetheless, given the clinical relevance of beat-to-beat FFR variation, potentially impacting clinical decision-making, such seems required to optimize its diagnostic value.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

Tim P. Van De Hoef, Martijn Meuwissen, Javier Escaned, and Jan J. Piek have served as speakers at educational events for Philips-Volcano, Boston Scientific and/or St. Jude Medical (now Abbott Vascular). Since completion of the study, Martijn A. Van Lavieren has moved to a position as employee of Philips, manufacturer of sensor-equipped guide wires.

DATA AVAILABILITY STATEMENT

Data available from the authors upon reasonable request.

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REFERENCES

1. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. EuroIntervention. 2019; 14(14):1435-1534.
2. Van De Hoef TP, Meuwissen M, Escaned J, et al. Fractional flow reserve as a surrogate for inducible myocardial ischaemia. Nat Rev Cardiol. 2013;10(8):439-452.
3. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360(3):213-224.
4. Xaplanteris P, Fournier S, Pijls NHJ, et al. Five-year outcomes with PCI guided by fractional flow reserve. N Engl J Med. 2018;379(3): 250-259.
5. Tarkin JM, Nijjer S, Sen S, et al. Hemodynamic response to intravenous adenosine and its effect on fractional flow reserve assessment: results of the adenosine for the functional evaluation of coronary stenosis severity (AFFECTS) study. Circ Cardiovasc Interv. 2013;6(6): 654-661.
6. Johnson NP, Johnson DT, Kirkeeide RL, et al. Repeatability of fractional flow reserve despite variations in systemic and coronary hemodynamics. JACC Cardiovasc Interv. 2015;8(8):1018-1027.
7. Smits P, Schouten J, Thien T. Respiratory stimulant effects of adenosine in man after caffeine and enprofylline. Br J Clin Pharmacol. 1987; 24(6):816-819.
8. Biaggioni I, Olafsson B, Robertson RM, Hollister AS, Robertson D. Cardiovascular and respiratory effects of adenosine in conscious man. Evidence for chemoreceptor activation. Circ Res. 1987;61(6): 779-786.
9. Watt AH, Routledge PA. Adenosine stimulates respiration in man. Br J Clin Pharmacol. 1985;20(5):503-506.
10. Escaned J, Echavarria-Pinto M, Garcia-Garcia HM, et al. Prospective assessment of the diagnostic accuracy of instantaneous wave-free ratio to assess coronary stenosis relevance: results of ADVISE II international, multicenter study (ADenosine vasodilator independent stenosis evaluation II). JACC Cardiovasc Interv. 2015;8(6):824-833.
11. Moody G, Mark R, Zoccola A, Mantero S. Derivation of respiratory signals from multilead ECGs. Comput Cardiol. 1985;12:113–116.
12. O'Brien C, Heneghan C. A comparison of algorithms for estimation of a respiratory signal from the surface electrocardiogram. Comput Biol Med. 2007;37(3):305-314.
13. Toth GG, Johnson NP, Jeremias A, et al. Standardization of fractional flow reserve measurements. J Am Coll Cardiol. 2016;68(7):742-753.
14. Seto AH, Tehrani DM, Bharmal MI, Kern MJ. Variations of coronary hemodynamic responses to intravenous adenosine infusion: implications for fractional flow reserve measurements. Catheter Cardiovasc Interv. 2014;84(3):416-425.

15. 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(4):1354-1367.
16. LeVarge BL, Pomerantsev E, Channick RN. Reliance on end-expiratory wedge pressure leads to misclassification of pulmonary hypertension. Eur Respir J. 2014;44(2):425-434.

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