size of the THV. One concern with overexpansion is impairment of proper leaflet function, resulting in significant central aortic regurgitation necessitating a second valve. We, however, saw no significant central insufficiency in any of our overexpanded S3 THV implants; our series from the 2 heart centers in Munich, Germany, encompassed more than 30 patients with initial deliberate overexpansion of the THV and more than 100 patients with subsequent post-dilation of a nominally deployed THV. S3 was originally not designed for overexpansion; however, we believe that the new frame geometry with a higher frame height and longer leaflets allows the S3 to be overexpanded to accommodate larger annulus sizes without causing significant central aortic insufficiency. It is also important to note that the valve frame foreshortens more when it is overexpanded, which may have implications for valve positioning.

Compared with the strategy of choosing the larger valve size and underdeploying it, the practice of selecting the smaller THV and overexpanding it, as noted above, may allow for a very safe and effective valve implantation with a lower risk of complications such as annular rupture. Furthermore, overexpanded THVs are more circular when fully deployed, which may have a positive impact on their durability, whereas the leaflets of the underdeployed valves may interact with the valve frame, leading to impaired durability.

Figure 2 provides the sizing chart for the S3 THV along with measurements for an overexpanded valve based on our current experience. We used measurements obtained during diastole for sizing because of the better image quality noted during diastole. It is recommended to use balloon sizing in cases where the annulus size falls in the "gray zone" between 2 valve sizes. In these gray zone cases, instead of selecting the larger valve size and underexpanding the valve, it may be preferable to select the smaller valve size and overexpand it with the addition of the pre-defined volume, especially when treating severely degenerated and/or calcified valves.

With this novel overexpansion concept, patients with an annulus size of up to 740 mm^2 (mean diameter of 31 mm) and more can be treated safely depending on the stiffness and degree of calcification of the native valve and annulus. It is important to note that overexpansion is limited by the burst pressure of the deployment balloon. Rupture of the balloon can increase the risk of embolization and stroke. Therefore, it is not recommended to add more than 2 to 4 ml of additional volume to the nominal deployment balloon volume for the given valve size. The addition of 2 extra ml of volume to the 23-mm, 3 ml to the 26-mm, and 4 ml to the 29-mm THV correlates with ~11% to 13% more volume in the deployment balloon for each valve size. Depending on the final diameter desired, it may also be possible to use less additional volume. In the future, benchmark tests are needed to confirm the long-term durability of an overexpanded S3 THV and viability of this strategy of overexpansion.

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REFERENCES

1. Webb J, Gerosa G, Lefevre T, et al. Multicenter evaluation of a next-generation balloon-expandable transcatheter aortic valve. J Am Coll Cardiol 2014;64:2235–43.

2. Kodali S. Clinical and echocardiographic outcomes at 30 days with the SAPIEN 3 TAVR System in inoperable, high-risk and intermediate-risk AS patients. Presented at the 2015 American College of Cardiology Scientific Sessions. March 15, 2015, San Diego, CA.

3. Kasel AM, Cassese S, Bleiziffer S, et al. Standardized imaging for aortic annular sizing: implications for transcatheter valve selection. J Am Coll Cardiol Img 2013;6:249–62.

4. Barbanti M, Leipsic J, Binder R, et al. Underexpansion and ad hoc post-dilation in selected patients undergoing balloon-expandable transcatheter aortic valve replacement. J Am Coll Cardiol 2014;63:976–81.

5. Blanke P. Influence of computed tomography-based over-sizing on the incidence of para-valvular regurgitation of a new generation transcatheter valve: Early results of the Intermediate Risk S3 Cohort PARTNER II trial. Presented at EuroPCR 2015. May 20, 2015, Paris, France.

ECG-Independent Calculation of Instantaneous Wave-Free Ratio

The instantaneous wave-free ratio (iFR) is a recently developed invasive index of coronary disease severity that simplifies stenosis assessment by eliminating the need for vasodilator administration (1–4).

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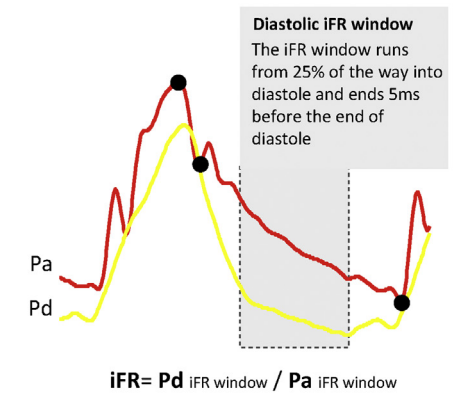
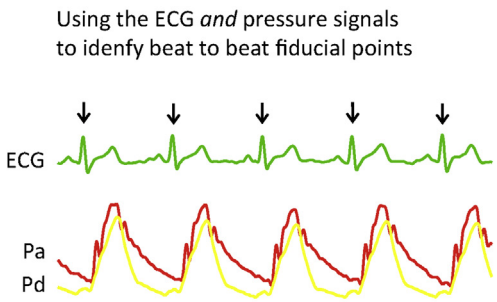
FIGURE 1 ECG-Independent Methodology for the Calculation of iFR



Identification of iFR window

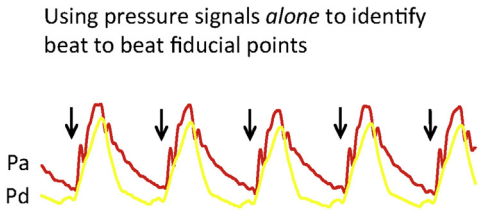
For accurate calculation of instant wave-Free Ratio (iFR) the correct window in diastole needs to be identified in each cardiac beat (grey box).

To achieve that consistently, a range of mathematical algorithms are used to analyze and identify various characteristic features of the pressure waveforms: peak, the dichrotic notch and the pressure nadir at the end of diastole (black dots).



Current iFR algorithm

Current iFR algorithm uses ECG *and* pressure signals (Pa and Pd) to detect fiducial points which identify each cardiac beat (black arrows). The ECG is used as a belt and braces approach to ensure specific time points in the pressure waveforms are correctly identified. This methodology is currently implemented in clinical iFR consoles and therefore require an ECG signal input from the patient for iFR calculation



New ECG-independent iFR algorithm

The new ECG-independent iFR algorithm uses the same mathematical algorithms over pressure waveforms, but no longer requires the additional step of the ECG gating to ensure correct beat identification.

This additional ECG step has now been removed, as beat to beat identification of each cardiac cycle can be reliably achieved with pressure waveforms alone (black arrows).

ECG = electrocardiographic; iFR = instantaneous wave-free ratio.

Multiple studies have so far compared iFR with other established invasive modalities such as hyperemic fractional flow reserve (FFR) and demonstrated it to be at least noninferior in its ability to detect vessel-specific myocardial ischemia (5,6) or flow limitation (7,8). iFR can also detect changes in stenosis hemodynamics after percutaneous intervention (9) and recently has been shown to provide useful pullback physiological information within a diseased vessel (3). Ongoing trials are evaluating the impact of iFR-guided revascularization on hard clinical outcomes (NCT02053038, NCT02166736, and NCT02015832).

iFR is calculated using conventional pressure guidewires as a ratio of coronary pressures (Pd/Pa) obtained during a specific period in baseline diastole, the wave-free period (1). Current iFR algorithms use both the electrocardiogram and coronary pressures as gating mechanisms to identify each cardiac beat

within a hemodynamic trace and the diastolic iFR window within each beat (1). The need for electrocardiographic signals from the patient is, therefore, a current requirement for iFR calculation (10) in clinical consoles.

Although current electrocardiography (ECG)-dependent iFR methodology has been demonstrated to be robust during both offline and real-time online measurements (10), a natural development of the technique would be to eliminate the need for electrocardiographic signals for its calculation, removing another procedural step and further simplifying the procedure. In the present study, we present an update in the development of iFR: a new methodology that uses only pressure signals for iFR calculation, aiming to further simplify the application of invasive functional assessment. The ECG-independent iFR calculation relies on the identification of specific end-systolic and end-diastolic waveform characteristics at both proximal (Pa) and distal (Pd) coronary pressure traces (**Figure 1**).

This study used a pooled sample of 320 coronary hemodynamic traces, representing all data from Imperial College NHS Trust used in previous multicenter studies in which our center participated (ADVISE [ADenosine Vasodilator Independent Stenosis Evaluation] study [1], ADVISE Registry study (2), and a study by Nijjer et al. [9]). The detailed methodology for data acquisition was reported previously (1,2). We tested the new iFR algorithm, which uses pressure signals alone (iFR-P) and compared it with the current methodology, which uses both electrocardiographic and pressure signals (iFR-ECG).

iFR-P and iFR-ECG derived almost identical numerical information. The correlation coefficient between methodologies was very high ($r = 0.9997$), with no numerical bias (mean difference = 0.0003) and minimal scatter (SD of the difference [SDD] between values = 0.004). For physiologically intermediate and mild stenoses, close to the iFR cutoff zone of 0.89 to 0.90, individual variability between iFR-ECG and iFR-P was even smaller (SDD = 0.0027 when iFR ≥0.80). As a result, when using an iFR-ECG cutoff of 0.89 as a reference standard to define physiologically significant lesions, there was no classification mismatch between modalities (area under the receiver-operating characteristic curve = 1). When the same iFR-P cutoff of 0.89 was tested to match an iFR-ECG of 0.89, sensitivity, specificity, negative and positive predictive values, and overall accuracy were all 100%. This is particularly important in light of ongoing clinical trials such as DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation; NCT02053038) and iFR SWEDEHEART (Evaluation of iFR vs FFR in Stable Angina or Acute Coronary Syndrome; NCT02166736) studies, which currently use the iFR-ECG algorithm and fixed iFR cutoffs to guide decision making. The results of these trials will therefore be directly applicable to the future use of ECG-free iFR in clinical practice.

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REFERENCES

1. Sen S, Escaned J, Malik IS, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the advise (adenosine vasodilator independent stenosis evaluation) study. J Am Coll Cardiol 2012;59:1392–402.

2. Petraco R, Escaned J, Sen S, et al. Classification performance of instantaneous wave-free ratio (ifr) and fractional flow reserve in a clinical population of intermediate coronary stenoses: Results of the advise registry. EuroIntervention 2013;9:91–101.

3. Nijjer SS, Sen S, Petraco R, et al. Pre-angioplasty instantaneous wave-free ratio pullback provides virtual intervention and predicts hemodynamic outcome for serial lesions and diffuse coronary artery disease. J Am Coll Cardiol Intv 2014;7:1386–96.

4. Petraco R, Park JJ, Sen S, et al. Hybrid ifr-ffr decision-making strategy: implications for enhancing universal adoption of physiology-guided coronary revascularisation. EuroIntervention 2013;8:1157–65.

5. van de Hoef TP, Meuwissen M, Escaned J, et al. Head-to-head comparison of basal stenosis resistance index, instantaneous wave-free ratio, and fractional flow reserve: diagnostic accuracy for stenosis-specific myocardial ischaemia. Eurointervention 2014.

6. de Waard G, Danad I, da Cunha RP, et al. Hyperemic FFR and baseline IFR have an equivalent diagnostic accuracy when compared to myocardial blood flow quantified by h215o pet perfusion imaging. J Am Coll Cardiol 2014;63(12_S). http://dx.doi.org/10.1016/S0735-1097(14)61695-8.

7. Sen S, Asrress KN, Nijjer S, et al. Diagnostic classification of the instantaneous wave-free ratio is equivalent to fractional flow reserve and is not improved with adenosine administration: results of clarify (classification accuracy of pressure-only ratios against indices using flow study). J Am Coll Cardiol 2013;61:1409–20.

8. Petraco R, van de Hoef TP, Nijjer S, et al. Baseline instantaneous wave-free ratio as a pressure-only estimation of underlying coronary flow reserve: results of the justify-cfr study (joined coronary pressure and flow analysis to determine diagnostic characteristics of basal and hyperemic indices of functional lesion severity-coronary flow reserve). Circ Cardiovasc Interv 2014;7:492–502.

9. Nijjer SS, Sen S, Petraco R, et al. Improvement in coronary haemodynamics after percutaneous coronary intervention: assessment using instantaneous wave-free ratio. Heart 2013;99:1740–8.

10. Petraco R, Al-Lamee R, Gotberg M, et al. Real-time use of instantaneous wave–free ratio: results of the advise in-practice: an international, multicenter evaluation of instantaneous wave–free ratio in clinical practice. Am Heart J 2014;168:739–48.