SUPPLEMENTARY DATA

PHYSIOLOGICAL ASSESSMENT OF CORONARY STENOSES

Pressure guidewires

They are 0.014 in guidewires with a pressure transducer where the radiopaque tip and body of the guidewire meet. They all allow disconnection from the transmitter so they can be used as working guidewires (figure 1 of the supplementary data).

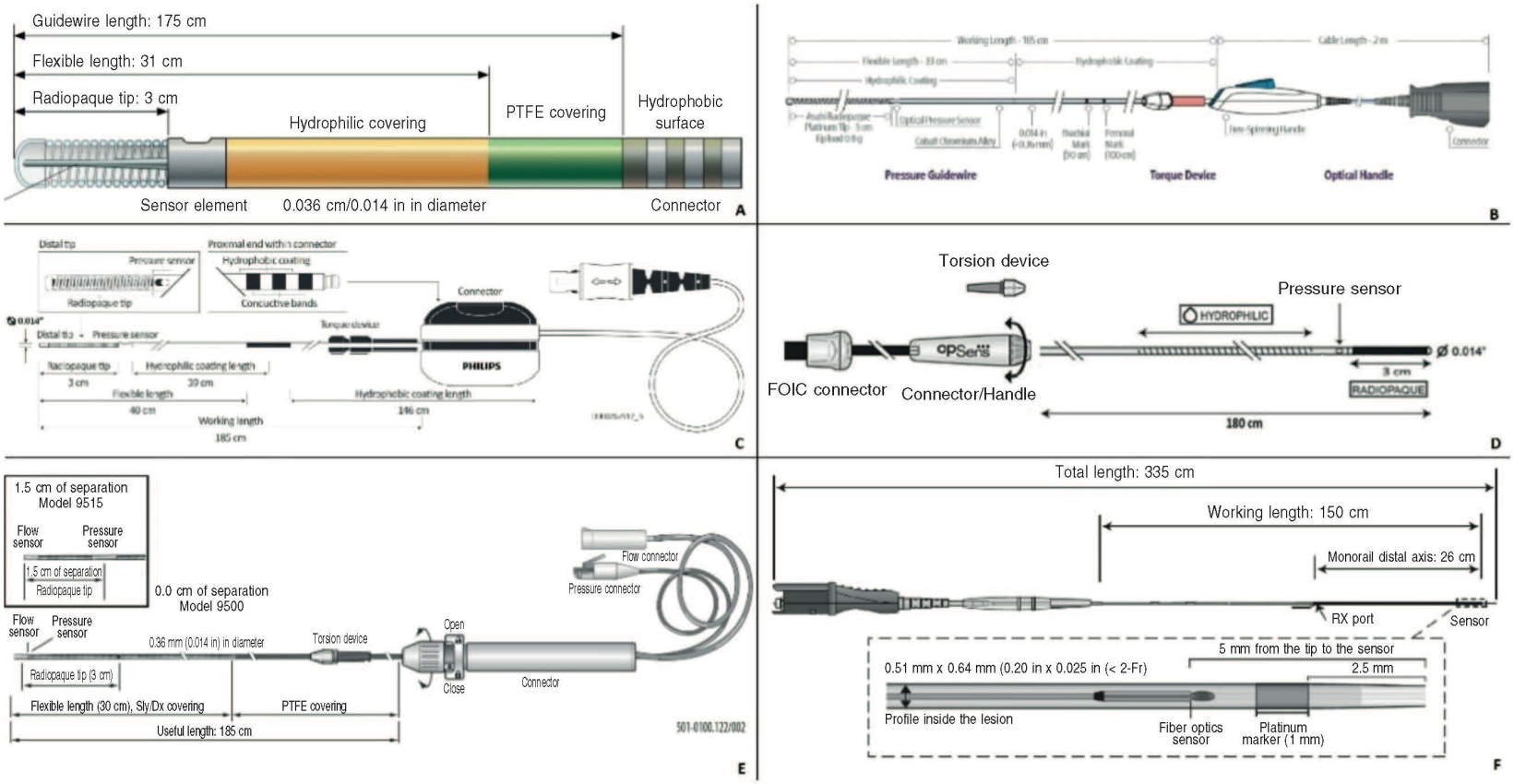

Figure 1 of the supplementary data. Technical characteristics of the different pressure guidewires available today. **A:** PressureWire X. **B:** Comet pressure guidewire. **C:** OmniWire pressure guidewire. **D:** OptoWire III pressure guidewire. **E:** ComboWire pressure guidewire. **F:** Navvus II catheter.

PTFE, polytetrafluoroethylene.

- **A. PressureWire X (Abbott Vascular, United States).** Only wireless pressure guidewire (5 m reach). It includes pressure and temperature sensors to measure pressure and flow using the thermodilution technique. Therefore, pressure indices like FFR, RFR, flow indices (CFR, coronary flow reserve), and resistance indices can be estimated by combing pressure and flow: index of microcirculatory resistance (IMR).[1]
- **B. Comet (Boston Scientific, United States).** Guidewire with an optic pressure sensor to measure FFR and DFR (diastolic hyperemia-free ratio). The way it is linked to the connector allows free guidewire turns for easier maneuvers.[2]
- **C. OmniWire (Philips, United States).** Pressure sensor to measure FFR and iFR. Also, it allows the coregistration of the angiography pullback by better locating pressure changes in the angiography.[3]
- **D. OptoWire III (Opsens, Canada).** Guidewire with an optic pressure sensor to measure FFR and dPR.[4]

- **E. ComboWire (Philips Volcano, United States).** Transducer pressure guidewire mounted close to the tip plus an ultrasound transducer on the tip. When used together with the ComboMap measurement system, it allows us to measure pressure and intracoronary blood flow at the same time.[5]
- **F. Navvus II (ACIST Medical Systems, United States).** It is a different alternative to distal pressure measurements. It is a coaxial microcatheter of < 2-Fr in diameter with a fiber optics sensor that can be mounted on any 0.014 in intracoronary guidewires. A working guidewire is advanced at distal level on which the microcatheter is mounted to measure the FFR and dPR. Pullback measurements can be taken without losing the position of intracoronary guidewire. A meta-analysis that assessed individual stenoses with the first version of this catheter showed a systematic bias by overestimating the severity of the lesions (the greater the lower the FFR), thus reclassifying the lesions in up to 18% of all the cases, and 23% in lesions with FFR values between 0.60 and 0.90.[6]

Step-by-step procedures

- **Guide catheter:** The size of the guide catheter needs to adjust to the size of the target ostium. If proper coronary flow is prevented, it can be detected through the ventriculization of the pressure signal Pa that becomes evident predominantly during hyperemia. This phenomenon will falsely increase the FFR value and underestimate the degree of myocardial ischemia.[7] Lateral hole catheters are ill-advised since a gradient between the lateral holes and the tip of the catheter can appear that becomes maximized when the FFR is measured.
- **Anticoagulation:** Secure it before the insertion of the guidewire—same as for an angioplasty—with weight-adjusted sodium heparin (70-100 IU/kg).
- **Hyperemia:** It is important to make sure that there is no epicardial vasospasm associated, which is why intracoronary nitroglycerin is often administered (left coronary tree: 200-300 µg; right coronary artery: 100-200 µg). The induction of maximum hyperemia is essential to measure the FFR while making sure that microvascular resistance is minimum and constant. The main drug used is adenosine that has a short half-life of 30 to 60 seconds). It is often administered through an IV infusion of a dose of 140 µg/kg/min. It can be administered through intracoronary doses of 100-200 µg for the right coronary artery and 200-300 µg para for the left one, and is better tolerated, faster, and more cost-effective.[7] Recently, a meta-analysis that studied 1413 lesions with 1972 individual measurements showed that there are no clinically significant differences between both methods.[8] The use of adenosine in infusion is mandatory when pullback measurements are going to be taken since hyperemia needs to be maintained for a longer period of time. Also, it is advisable in aorto-ostial lesions though it can be delivered via intracoronary route of administration or after decannulation.

Pressure guidewire (resting indices, FFR)

1) Catheterize the target artery with a conventional guide catheter making sure that aortic pressure won't drop during catheterization.
2) Anticoagulation with sodium heparin (70-100 IU/kg).
3) Administer 100-300 µg of intracoronary nitroglycerin.
4) Execute zero of aortic pressure in the cath lab polygraph making sure that all connections are properly adjusted.
5) Connect and equalize the pressure guidewire at room temperature.
6) Advance the guidewire until the sensor rests at the same level of the tip of the guide catheter.
7) Remove the guidewire introducer sheath and wash the guide catheter with a saline solution
8) Equalize/normalize pressure guidewire with that of the catheter in the console making sure that both pressure waves are the same.
9) Advance the guidewire until 2-3 cm distal to the lesion or the target region.
10) Remove the guidewire introducer sheath once again (re-insert it if necessary) and wash the guide catheter with a saline solution.
11) Regarding resting indices, select one in the console and take the measurement then.
12) To measure the FFR, change the mode of the console to FFR, and administer intracoronary (200 µg for the left coronary artery, 100 µg for the right coronary one) or IV adenosine (140 µg/kg/min). When using intracoronary adenosine, consider the FFR the lowest Pd/Pa ratio (distal/aortic coronary pressure ratio) obtained after inducing hyperemia (usually 15 to 20 seconds). With IV adenosine, wait until stable hyperemia is achieved for another 90 to 180 seconds of infusion, and obtain the lowest Pd/Pa ratio.
13) To study the distribution of stenoses along the vessel, the resting indices allowing pullbacks can be used like the iFR and the RFR or else with the FFR if the continuous infusion of adenosine is used. Guidewire is then slowly removed while keeping hyperemia and simultaneously seeing the location of the guidewire though fluoroscopy. In case of diffuse lesions, the gradual recovery of pressure along the vessel will be seen. In case of focal stenosis, a sudden

increase of pressure proximal to the lesion can be seen. The exact spot of the lesion can be confirmed by moving the guidewire backwards and forward in the region of interest.

14) Confirm the guidewire transducer lack of drift in the initial position. If pressure drift is > 2-5 mmHg, normalization followed by another measurement are advised.

15) Remove the intracoronary guidewire and perform the angiography to confirm the lack of complications.

Problems, causes, and solutions

A few procedural details should be taken into consideration to obtain measurements that should be as reliable as possible. We need to make sure that all connections have been properly adjusted and that the guidewire introducer sheath has been removed when taking the measurements since it can falsely reduce the aortic pressure. The guide catheter needs to be washed with a saline solution to prevent dampened aortic pressure. Also, we need to make sure that during acquisition no variations associated with breathing, cough or arrhythmias exist.

Damping of aortic pressure by the guide catheter can occur with catheter of a larger diameter (7-Fr-to-8-Fr) in the presence of ostial lesions or with small-caliber epicardial vessels. In such cases, it is advised that the guide catheter should be out of the coronary to obtain an actual measurement of aortic pressure both during equalization and the measurement of pressures.

Lateral hole catheters can create a pressure gradient between the aorta and the catheter that may go unnoticed until hyperemia is induced. If they need to be used, it is essential to unhook the catheter from the coronary artery when taking the measurements. When these catheters are used intracoronary adenosine should not be administered since part of the dose would fall directly into the aorta.

The presence of drift can be suspected when, although there may be different pressures between proximal and distal measurement, the shape of the distal wave keeps its dicrotous fissure since significant stenoses act as a high-frequency filter complicating the transmission of the signals causing the presence of such fissure. Drift is more common after connecting/reconnecting the guidewire, especially after the angioplasty or after prolonged use; fiber optics-based guidewires and catheters have less drift compared to those that use piezoelectric systems.

Spasm and pseudostenosis: passing the intracoronary guidewire can produce coronary spasms, which is why it is important to administer intracoronary nitroglycerin even in patients with low pressures since low doses of nitroglycerin (50-100 µg) are well tolerated. The passage of the guidewire can correct tortuous arteries generating the well-known «accordion effect» that would trigger falsely altered measurements, which is why it

is important to perform the angiography with the guidewire already passed through tortuous arteries and then compare it to the guidewire-less angiography; in these cases, reliable measurements of distal pressure cannot be taken.

Hydrostatic pressure effect: when measuring pressure, it is often assumed that all transducers can be found at the same height as the heart, which is what happens with equalization. However, when taking measurements from the distal left circumflex artery or distal right coronary artery there is certain hydrostatic pressure that could increase the measurement of Pd/Pa in 0.01-0.04 points; this is particularly evident in arteries without stenosis.

Central venous pressure (CVP) effect: in practice, it is considered that venous pressure is negligible, which is why the original formula of FFR (Pd-CVP/Pa-CVP) is simplified into Pd/Pa. An increased CVP reduces FFR. However, since the studies conducted so far have overlooked the effect of CVP, its measurement is not necessary in cases of stable angina. It could be considered valuable in patients with heart failure or hypotension in whom the influence of CVP is greater.

Limitations of the methods to induce hyperemia: methylxanthines like caffeine, theobromine (chocolate), and theophylline are competitive antagonists of the adenosine receptor. That is why it is advised not to use them 24 hours prior to a study where adenosine will be used to obtain a proper hyperemic response. The intracoronary administration of adenosine or infusion at higher doses (210 µg/kg/min) can reduce, at least partially, the effect of caffeine; tolerance at higher doses of adenosine is lower with the appearance of more adverse events.[9]

Specific clinical settings

- **Diffuse coronary artery disease:** performing a continuous pullback at a speed of ± 1 mm/s of the pressure guidewire from distal to proximal can help us identify a focal region of stenosis (sudden pressure increase) or the presence of diffuse atherosclerosis where the recovery of pressure is gradual across the entire artery. This information can help us determine the utility of the angioplasty. In some cases, a focal lesion overlapping the diffuse stenosis that needs to be treated can be found. An objective way to quantify spatial damage is the *pullback pressure gradient (PPG*) that is based on the measurement of the maximum loss of FFR in 20 mm of the vessel, and the length of the epicardial coronary segment with FFR impairment. This is a continuous measurement where values close to 1,0 represent focal lesions while those close to 0 represent diffuse damage.[10] Although the technique was developed with automatic guidewire pullbacks, its feasibility has been recently demonstrated with manual pullbacks.[11]
- **Ostial lesions:** it is useful to assess aorto-ostial lesions mainly in jailed lateral branches that are hard to assess on the angiography. In a study of 94 lesions in jailed branches, only 72% of the lesions with stenoses > 75% on the QCA were significant according to FFR while no lesions with stenoses < 75% presented FFR < 0.75.[12] When dealing with aorto-ostial lesions it is important to remove the guide catheter from the ostium both for equalization and measurement purposes to prevent the catheter from blocking coronary flow.
- **Aortic stenosis:** too many patients with aortic stenosis also have coronary artery disease Severe aortic stenosis creates augmented microvascular resistances, and a reduced vasodilator reserve that can affect the FFR measurements. In patients in whom FFR was measured before and after transcatheter aortic valve implantation (TAVI) with intracoronary adenosine, only minor changes were seen in FFR values suggesting the safety and validity of FFR studies in these patients. The approach here changes in nearly 15% of the patients especially in intermediate lesions on the angiography.[13]
- **Acute coronary syndrome (ACS):** after an acute myocardial infarction, the predictive capabilities of the FFR have some theoretical limitations. Due to microvascular damage, response to hyperemic stimuli is variable, flow through stenosis is reduced, and the FFR goes up. In the STEMI stetting, when studying a non-culprit lesion, a low FFR is indicative of significant stenosis; although a normal FFR could be inconclusive, the probability that we're

dealing with a severe lesion with FFR > 0.80 is low.[14] In the FAME trial, patients with unstable angina or STEMI in whom revascularization was FFR-guided experienced a relative reduction of the risk of major adverse cardiovascular events of 19% compared to angiography-guided revascularization. A similar benefit was reported in patients with stable angina (absolute risk reduction of 5.1% vs 3.7%; *P* = .92), and less need for stenting too.[15]
Numerous studies have demonstrated that revascularization of non-culprit vessels in patients with STEMI reduces adverse events, and that the use of the pressure guidewire reduces the number of revascularizations at follow-up (12.5% vs 25.2%; HR, 0.45; 95%CI, 0.31-0.64; *P* < .001) on top of reducing the number of stents implanted with the corresponding economic benefit.[16]

Myocardial ischemia induces microvascular dysfunction not only in the territory supplied by the culprit artery,[17] which can lead to false negative FFR measurements. The FFR cut-off value in patients with ACS is still controversial; the study conducted by Hakeem et al.[18] proved that patients with FFR < 0.85 had more adverse events. The iFR at follow-up, if measurement is taken 16 days later, is significantly higher compared to the acute moment (+ 0.03; *P* ≤ .001).[19] The opposite happens with the evolution of FFR: 1 month after STEMI a significant reduction of FFR can be seen (−0.03; *P* = .001) with a stable iFR (+ 0.012; *P* = .12) in probable association with an increased hyperemic microvascular resistance,[20] which is suggestive that non-hyperemic indices are a better option in the ACS setting.

An analysis of individual data from 5 large studies (8579 patients) reveals that, compared to stable angina, the safety of delaying revascularization in ACS using FFR is lower; however, treatment does no seem to reduce the number of major events.[21] A study conducted in patients with STEMI and multivessel disease that assessed non-culprit lesions with FFR showed a greater number of events in those patients revascularized based on FFR > 0.80 compared to those revascularized based on angiography.[22] These results exemplify diagnostic complexity in the ACS setting.

- **Measurement after coronary angioplasty:** obtaining postoperative FFR proves that there is a correlation among suboptimal results, residual disease, and prognosis.[23] Two studies, the FFR SEARCH (Fractional flow reserve–stent evaluated at Rotterdam Cardiology Hospital)[24] and the Target FFR (An evaluation of a physiology-guided PCI optimisation strategy)[25] demonstrated that up to 68% of the patients treated of a coronary lesion still have some lesion with FFR ≤ 0.90 while 11% of them still have lesions with FFR ≤ 080. There is an inverse, continuous and independent correlation between postoperative FFR and the appearance of events (HR, 0.86; 95%CI, 0.80-0.93; *P* < .001).[26] The optimal postoperative FFR to reduce events should be > 0.85.[23] Regarding resting indices, a Pd/Pa ratio > 0.96 is associated with FFR values > 0.86 and with a lower rate of adverse events.[27]

Physiological results depends on various factors including the stent length and diameters, as well as damage to the left anterior descending coronary artery. In case of resting indices, the DEFINE-PCI trial (Physiologic assessment of coronary stenosis following PCI) proved that 24% of the patients had residual ischemia (iFR ≤ 0.89) after successful angioplasty with 81.6% of the cases attributed to angiographically non-visible focal lesions. Postoperative iFR ≥ 0.95 was associated with better 1-year event-free survival and a greater reduction of angina symptoms,[28] which proves just how important it is to assess procedural results using physiology.

Angiography-derived indices. Practical management (QFR, FFRAngio, vFFR)

The different systems available for the non-invasive use of FFR share many similarities in practice. To simplify and as an example we present the steps that should be followed for the functional assessment of an epicardial lesion through QFR since it is the most widely studied technology in medical literature.

After the administration of intracoronary nitrates, 2 angiographic views separated at least 25° are acquired where the target stenosis can be seen without structure overlapping or shortening. End-diastolic frames will be selected wherever contrast may have filled up the artery completely so contouring can be performed (figure 2 of the supplementary data).

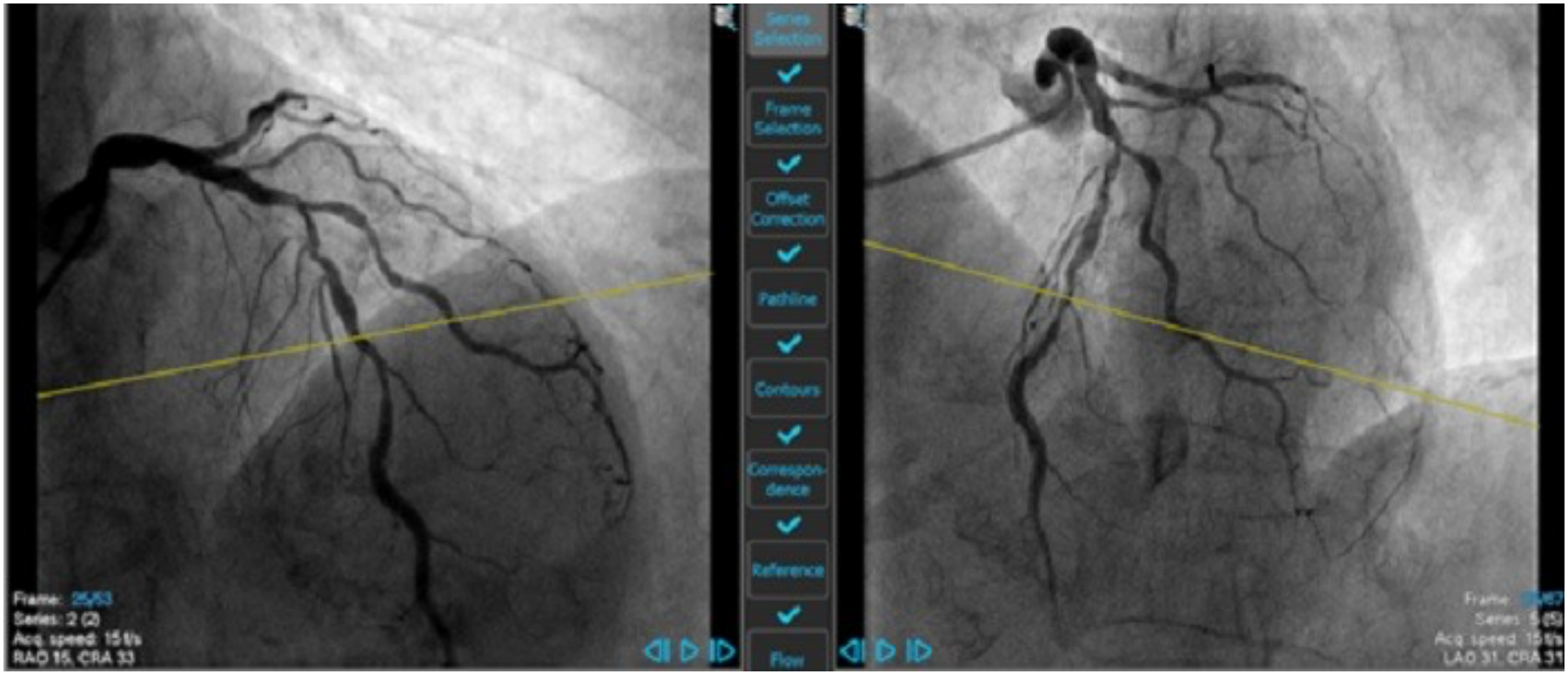

Figure 2 of the supplementary data. Two views showing a lesion in the mid left anterior descending coronary artery with different angles with a properly filled artery.

Anatomical sites of start, end, and reference in both views are determined. Also, the contouring is drawn automatically although it can be corrected manually if required (figure 3 of the supplementary data, dot #2).

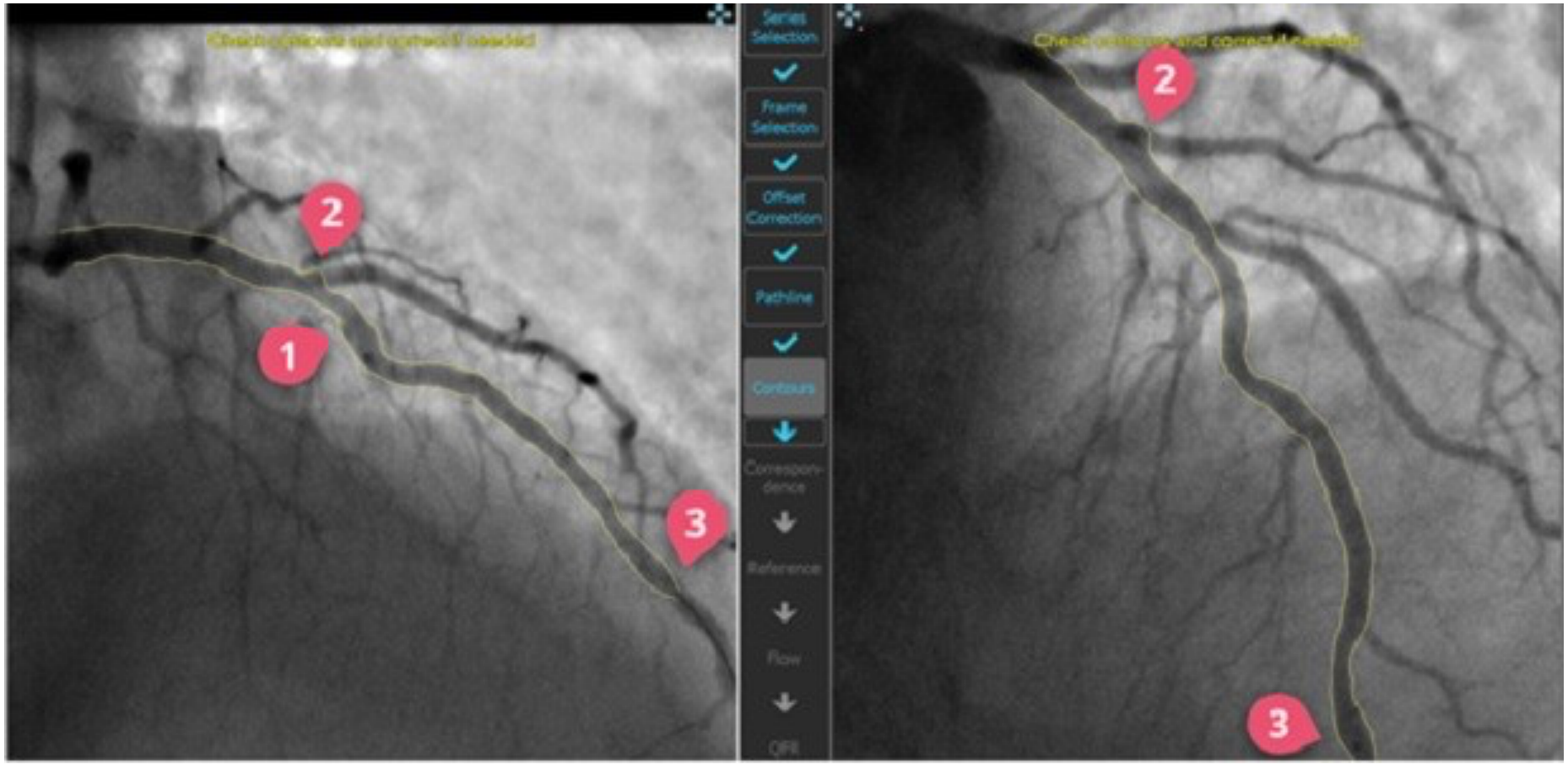

Figure 3 of the supplementary data. Automated contouring of left anterior descending coronary artery. Dot #2 shows where manual correction is needed. Afterwards, the match between the arterial diameters of both views should be checked (except for eccentric lesions) and the borders of the lesion should be established (figure 4 and figure 5 of the supplementary data).

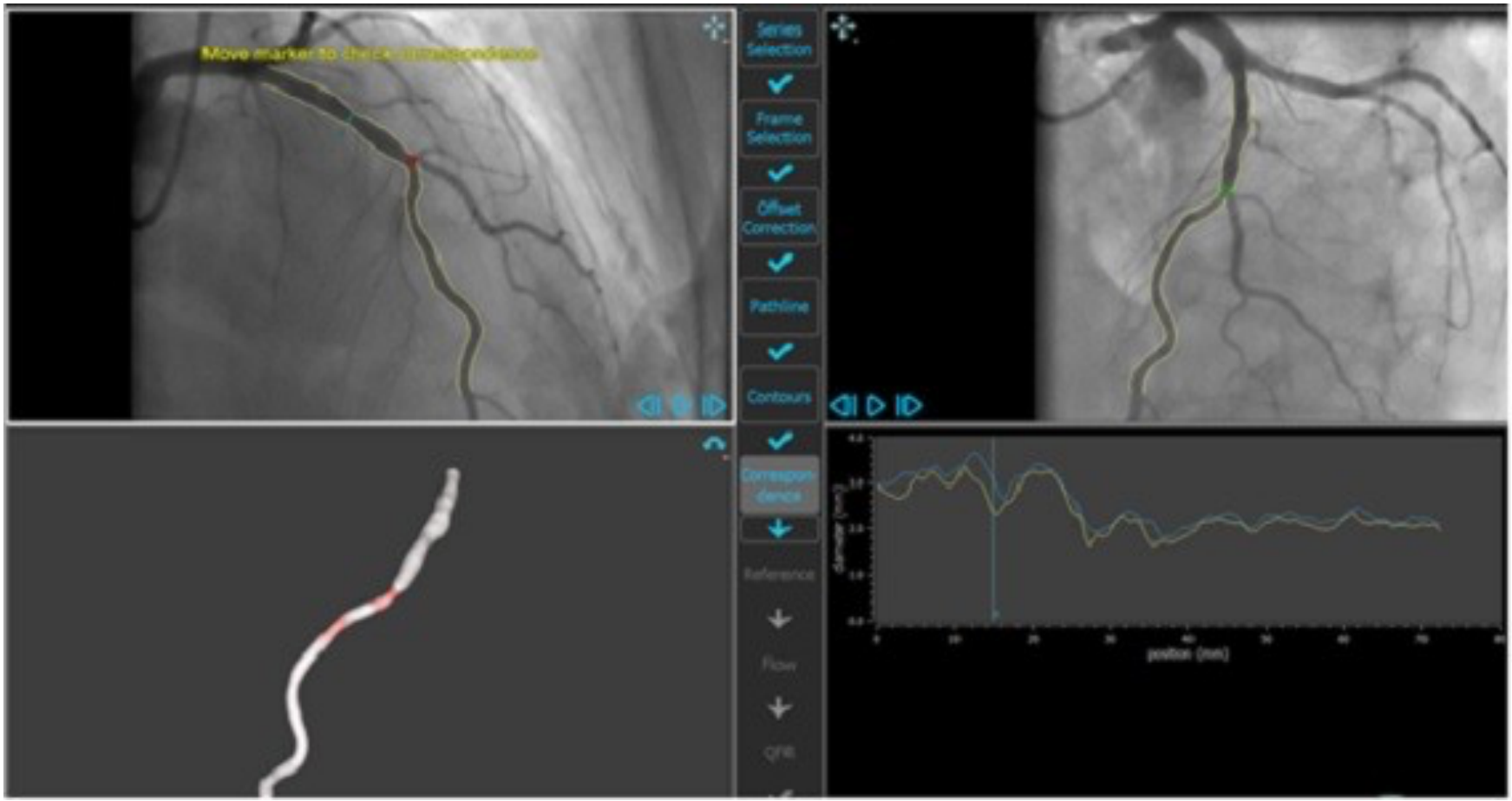

Figure 4 of the supplementary data. Determination of lesion borders and diameter check in both views.

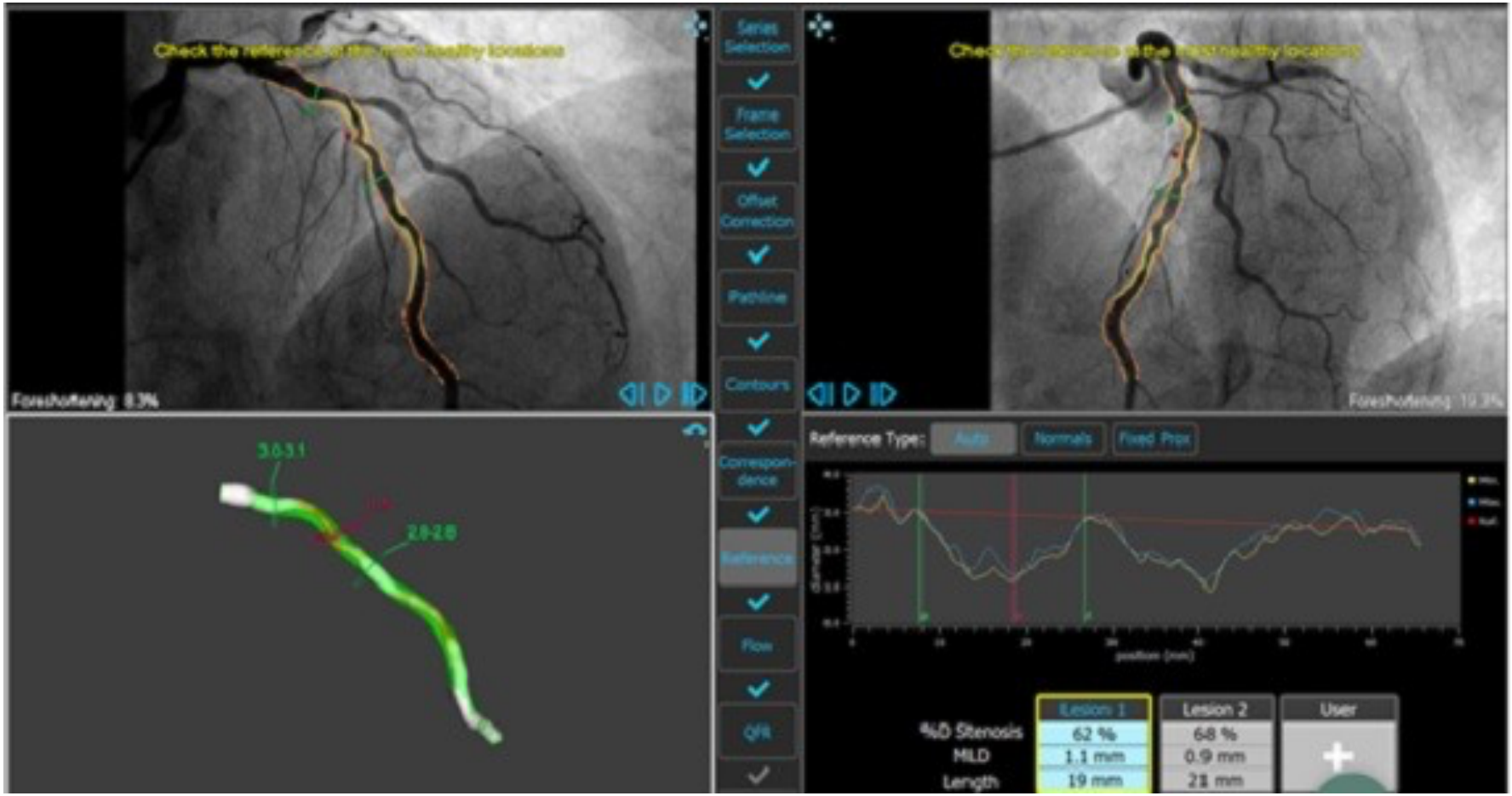

Figure 5 of the supplementary data. Anatomical result of contouring.

Eventually, the system offers the option to choose the flow estimate model (figure 6 of the supplementary data).

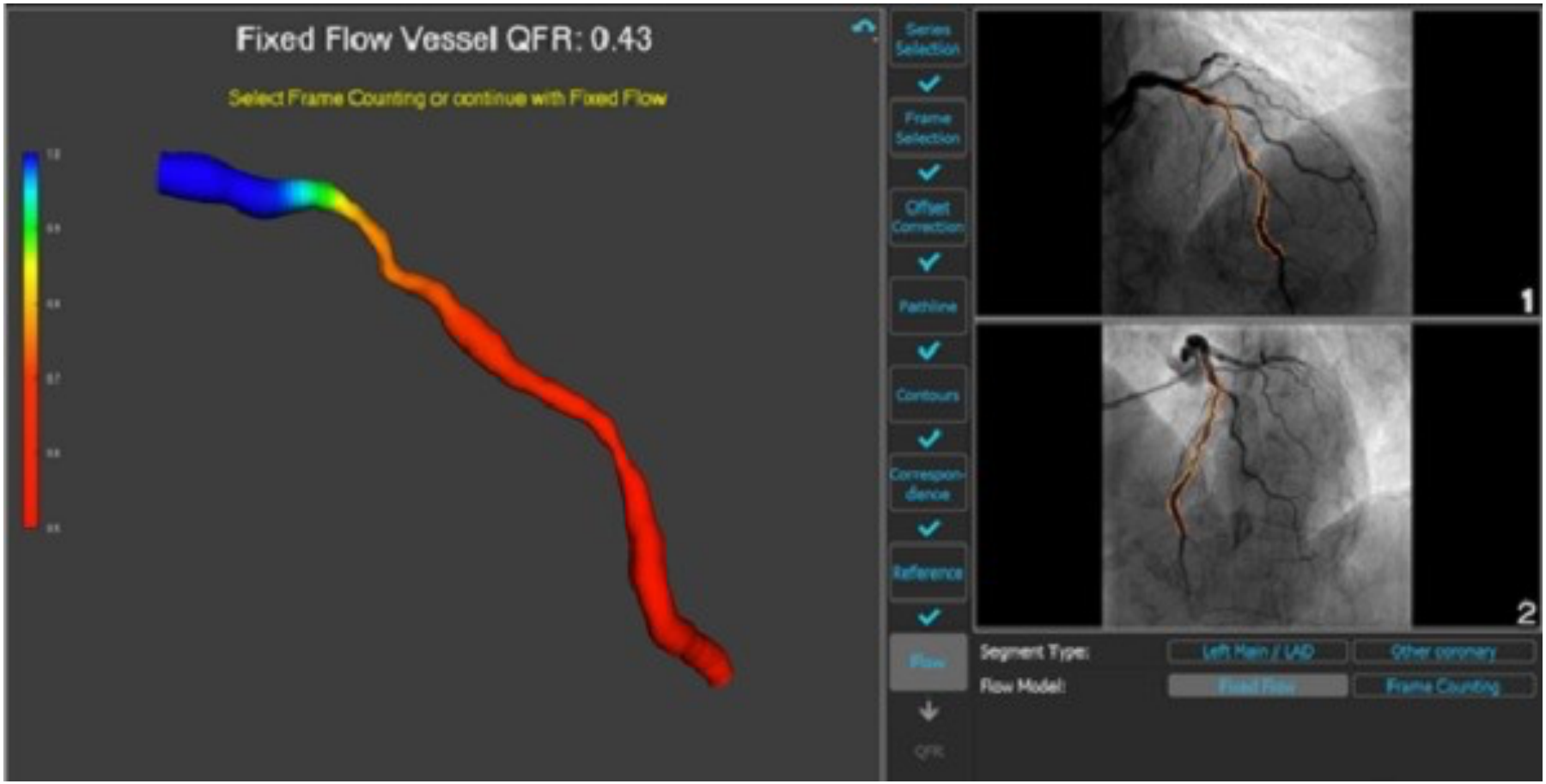

Figure 6 of the supplementary data. Provisional results; the flow estimate method can be selected here.

Once the steps have been completed, a report is opened including the QFR values and the references in diameter and length of the stenoses that should be evaluated.

PHYSIOLOGICAL ASSESSMENT OF CORONARY MICROCIRCULATION

Invasive indices

Thermodilution

Bolus (CFR, IMR)

1) Catheterize the target artery with a conventional guide catheter (6-Fr) making sure that aortic pressure does not drop with catheterization.
2) Anticoagulate with sodium heparin at 70-100 IU/kg.
3) Administer 100-300 µg of intracoronary nitroglycerin.
4) Execute zero of aortic pressure, activate the CoroFlow console (Coroventis Cardiovascular System, Sweden) to connect the PressureWire X and switch on the guidewire transmitter.
5) Advance the guidewire until the pressure sensor is found at the same level as the tip of the guide catheter.
6) Remove the guidewire introducer sheath and wash the guide catheter with a saline solution.
7) Equalize the guidewire pressure with that of the catheter in the console making sure that both pressure waves are the same.
8) Advance the guidewire until the distal third of the target artery.

9) Remove the guidewire introducer sheath once again and wash the guide catheter with a saline solution.

10) Change to CFR/IMR mode in the CoroFlow console.

11) Administer a bolus of 3 mL of physiological saline solution with the Luer-lock syringe (5 mL to 10 mL) at room temperature through a guide catheter rapidly closing the side stopcock. Repeat the bolus 2 more times based on the indications of the CoroFlow console making sure that the 3 measurements of the mean transit time do not have a variation > ± 10% among them.

12) Start the IV infusion of adenosine at doses of 140 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and wait 2 min to achieve stable hyperemia.

13) Perform 3 new injections of saline solution at room temperature as in step #12.

14) FFR, IMR, and CFR values are estimated automatically by the CoroFlow console.

15) Remove the intracoronary guidewire and perform an angiography to confirm the lack of complications.

Continuous (flow and absolute y resistance)

This system requires a continuous infusion pump to infuse a saline solution up to 30 mL/min and facilitates estimates with the CoroFlow system (Coroventis Cardiovascular System, Sweden) that has a receptor to capture the signal of the PressureWire X. Microvascular resistance > 500 $mmHg \cdot l^{-1} \cdot min^{-1}$ (Wood units, WU) measured at left anterior descending coronary artery proximal level properly predicts the presence of microvascular dysfunction.[29]

1) Place the PressureWire X as shown in steps #1 to #8 of the previous section.

2) Disconnect the PressureWire X transmitter without switching it off.

3) Connect the proximal border of the RayFlow catheter to the extension of the infusion pump. Purge the catheter until 4 jets come out of its distal border.

4) Introduce the distal border of the guidewire into the monorail of the RayFlow catheter.

5) Connect once again the guidewire transmitter.

6) Advance the RayFlow catheter on the guidewire until the left anterior descending coronary artery proximal segment keeping the tip of the guidewire where it was previously located. The guidewire sensor should be placed, at least, 50 mm distal to the microcatheter radiopaque mark.

7) Select the Abs mode in the CoroFlow console. Execute zero temperature.

8) Start recording in CoroFlow (REC).

9) Start infusion of saline solution at room temperature with pump at 15-25 mL/min (P_{max} < 600 PSI) until reaching a stable temperature drop (30 to 60 s). The velocity of infusion of the saline solution should be indicated in the console.

10) Remove the guidewire at constant speed until introducing the temperature sensor inside the microcatheter with which the temperature at which the saline solution reaches the tip of the catheter is obtained.

11) Stop the infusion of the saline solution and wait until baseline temperature gets back into the curve (T = 0).

12) Stop recording (STOP) with which automatic measurement of absolute resistance (R_{abs}), absolute flow (Q_{abs}), and FFR is obtained. We need to make sure that the console reads the speed of infusion of the saline solution we've been working with.

13) Additionally, the same measurements with an infusion rate of 5-10 ml/min can be obtained, which allows us to estimate the absolute coronary flow at rest with which the coronary flow reserve can be estimated. This distal measurement should be obtained in the artery and the tip of the microcatheter. For estimation purposes the speed of infusion should be specified in the console.

14) Remove the intracoronary guidewire and perform an angiography to confirm the absence of complications.

Doppler (CFR, HMR)

1) Follow steps #1 and #3 as described to perform thermodilution in boluses.
2) Execute zero of aortic pressure.
3) Connect the ComboWire to the ComboMap console and progress it until the pressure sensor is in the tip of the guide catheter.
4) Remove the guidewire introducer sheath and wash the catheter with a saline solution.
5) Equalize the guidewire pressure with the catheter in the console making sure that both pressure waves are the same.
6) Advance the guidewire until the distal third of the target artery while making sure there is a proper Doppler wave in the console for which the sensor needs to be coaxial to flow and the guidewire very stable.
7) Optimize the signal/noise ratio in the console by modifying the instantaneous maximum velocity limit. In most cases the self-adjustment option is effective.
8) Measure flow velocity and the correlation of baseline pressures in the console.
9) Administer adenosine in infusion or intracoronary, and measure FFR, CFR, and hyperemic microvascular resistance (HMR).
10) Remove the intracoronary guidewire and perform an angiography to confirm the absence of complications.

Angiography-derived indices. Practical management (IMRangio)

In practice, we should mention how easy it is to determine with proper access and training with already validated software tools (QAngio from Medis or FlashAngio from Rainmed), angiographies, and arterial pressure data. Currently, several formulae exist for its estimate that vary based on the study group and the software used with which the value can be obtained in a matter of minutes after the angiography just by following the steps previously reported to obtain QFR or angio-FFR and completing the formula with the necessary data.

However, currently, IMRangio is not systematically obtained in the routine clinical practice. Still, it is anticipated that, in time, it will because it is easy to obtain, procedure is safe, and the aforementioned data back it up.

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