

The assessment of coronary flow reserve should be an integral part of stress echo

Agonist

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Ischaemic heart disease is the expression of an anatomical disease and also a suffering whose study requires a thorough analysis of coronary and myocardial function, beyond luminography which is provided by cinecoronariography or the state of the arterial wall and plaque which is informed by multislide tomography.

From Gould's classical works, we know that in most of the patients basal coronary flow does not significantly decrease until a 90% of the lumen is blocked, while coronary flow reserve (CFR), as an expression of the difference with the maximum flow reached, begins to be altered with stenosis from 40% and it is evident with 70% of obstruction. (1)

According to the results of different clinical studies, its determination is essential for the functional assessment of a coronary stenosis. (2)

Graduated stress test, which is used in the daily practice, assesses indirectly CFR through the behavior analysis of ST and symptoms.

The major return of graduated stress test is obtained in patients with basal ECG which is interpreted with results of low and high risk; however, it is with intermediate risk (40-50% in most of the series) where tests with images have more impact when restratifying patients in extremes to decide the most appropriate therapeutic behaviors.

The addition of images is also justified in those patients who may have a false negative in the ECG analysis, as in young women, patients with mitral valve prolapse, previous medication, hypertrophic ventricles, in patients with a doubtful ergometry and when a more specific prognostic stratification is needed after an acute coronary syndrome.

Exercise echo in its different methods (erect bicycle, sliding band and supine stretch) is the first election method of stress-echo menu and nobody may dispute the huge value of its information, even in absence of symptoms and without changes in ST-T. (3)

The preference for physical coercion is supported in that it is considered the most physiological of the tests and in the additional information that it contributes about cardiovascular state, but it has a higher complexity level than pharmacological stress echo due to major technical difficulties for its realization and interpretation.

Around 30% of patients are not prepared to carry out physical coercion and/or they may not complete it until submaximal frequencies; besides, the inadequate interpretation decreases the diagnostic sensitivity and this is common in operators with lack of experience in the technique of rapid acquisition of images or in presence of suboptimal ultrasound window (5-10% of the patients), especially if contrast agents to enhance the endocardium are not available.

Pharmacological stress echo is an alternative when the realization of an effort test is not feasible, when it is contraindicated or when the patient may not carry out enough effort and/or when the window is not suitable.

The drug election for the procedure (dobutamine, dipyridamole or adenosine) will depend on the experience and center resources, characteristics of the patient in relation to his clinical situation, ventricular function, previous medication and especially contraindications for each drug in particular.

From multiple comparative studies between dobutamine and dipyridamole to show superiority from one modality over the other in the detection of new parietal abnormalities, dobutamine showed a superior sensitivity (in vessel disease) and a major specificity with dipyridamole; however, the accuracy is similar.

Therefore, in the best case we will find a false positive study and a false negative study every ten tests of pharmacological stress echo and with certainty, diagnostic mistakes are even bigger, especially in difficult patients (with LBBB, arrhythmias, hypertrophic ventricles) in some laboratories.

Another inherent limitation to the methodology is the subjectivity of the interpretation in parietal contractility through visual analysis which is still the art state according to the last European Association of Echocardiography and American Society of Echocardiography guideline recommendations. (4, 5)

We continue in the search for more objective techniques and although the potential of tissue Doppler, 2D strain and 3D electrocardiography to increase sensitivity and diagnostic specificity are appreciated, these methods are still in assessment and they are not systematically used.

The determination of CFR by transthoracic

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echocardiogram is nowadays an important tool which is validated and supported by multiple trials for the study of coronary function. (6)

We have at hand a diagnostic and prognostic tool which is scientifically supported in an old physiopathological concept. (1)

For 10 years, we use this information which is backed up by the good correlation with other invasive techniques with low-cost advantages, simpleness and reproducibility during pharmacological stress echo in our laboratory. (7)

The possibility to determine the distal anterior descending artery flow (AD) and its CFR exceeds 95% of assessed patients; it is less in the posterior descending artery (PD) with a 70% of success, while in the territory of circumflex artery (Cx) feasibility ranges between 50% and 60%. (8)

Nowadays, the transducer should not be changed to visualize different arteries due to the presence of new matrix transducers 4-2 MHz and modern equipments have a predetermined "searcher" to analyze coronary flows. The study of the coronary tree, at the mid-distal level of the three main branches in half of the patients, is possible with vasodilators. With dobutamine, we may only assess AD territory, since intense hyperkinesis and translation movements of RCA and Cx block the obtaining of good images during stress peak.

From the different ways of measuring CFR, the most used is the calculation of diastolic velocity relationship between stress peak and basal velocity (normal ≥ 2).

Before the calculation of CFR, the assessment of systodiastolic relationship of velocities in rest in AD is a good practice, due to when its value is < 1.6 there could be a significant obstruction (normal ≥ 2) and the biggest path of coronary territories in search for turbulent flows with very high velocities and gradients among adjacent regions should be covered; velocities that are doubled in neighboring zones strongly suggest the diagnosis of significant stenosis in the assessed region.

Transthoracic echo is also a sensitive and specific method for the diagnosis of AD and RCA occlusions over the base of the analysis of the direction of epicardial flows, but undoubtedly the major information is obtained with the determination of CFR which gives us objective numerical information, with additive value to the analysis of contractility in pharmacological stress echo.

A meta-analysis performed by Rigo (9) over the diagnostic value of stress echo with dipyridamole, which includes our own experience, shows that sensitivity according to the analysis of contractility is increased with additional information of CFR from $67\% \pm 9\%$ to $90\% \pm 3\%$, with little loss of specificity. (9)

There are not enough references about dobutamine, but in a standard work (published by JACC in 2001)

Takeuchi showed a feasibility of 90% to assess CFR in the AD (similar to the sample), with good correlation between peak value in the motility index and CFR in stress peak and he also checked that diagnostic accuracy is improved in studies in which the analysis of parietal motility in AD territory is complicated.

In Clínica de Mayo, Pellikka's team showed the additional value when measuring CFR during dobutamine test to improve the detection of myocardial ischemia, and although its use is recommended to improve the detection of myocardial ischemia, it is not used in the daily practice (another example of "the two faces of Juno"), many times which is published as valuable is not what it is done at the own laboratory. (10)

In our daily practice, with thousands of studies already done, we prefer to analyze the assessment of CFR with dipyridamole due to it has a long mean life, a small increase of the heart rate, due to it is more feasible in the determination in the three coronary territories and due to results are more exact when the Doppler sample is at the same place during the whole procedure. (11)

Due to most of the pharmacological studies in our country are requested with dobutamine, our experience and feasibility have been increased in the last years, even with the problem of the main technical difficulties.

In the daily practice, we use either of the two drugs for the following instructions: 1) determination of CFR for the detection of lesions which are functionally significant, 2) assessment of functional significance of intermediate obstructive lesions (50-70%) in AD territory, (12) 3) assessment of results in surgical interventions and postangioplasty, 4) study of ischemic patients with angiographically normal coronary arteries, 5) in patients with LBBB, where contractility is difficult to assess, in order to determine and/or rule out the ischemic etiology, 6) in the assessment post-AMI to determine microvascular integrity and 7) differential diagnosis of dilated cardiomyopathy.

There are other scenes in which there are evidences of their usefulness but we do not have a systematic monitoring, as it is in the determination of functional significance in muscular bridges, in the monitoring of medicamentose therapeutical actions and/or physical exercise, for the assessment of transplanted and chagasic patients, in the study of microvascular disease (diabetic and hypertensive patients) and in hypertrophic cardiomyopathy.

A $CFR \geq 2$ rules out a functionally significant stenosis in the studied territory, but its reduction is not always specific of coronary stenosis and it may be influenced by multiple hemodynamic variables and/or associated pathologies; however, values < 2 , in most of the patients, are secondary to severe coronary lesions.

Apart from the indisputable diagnostic usefulness,

the determination of CFR have shown that it has a prognostic value regardless of clinical variables and the result of the analysis of parietal contractility.

Rigo et al. were the first in checking that CFR during stress echo with dipyridamole adds a prognostic value, even in the group of patients with normal contractility. (13)

According to a recent publication of Cortigiani's team, the assessment of CFR of AD and RCA allows them to identify different prognostic variables. In particular, preserved CFR in both vessels was highly predictive with favorable evolution, while reduced CFR in one of the two arteries, especially in AD, was a strong marker of future events. (14)

In our own experience, in a recent work, we could show that in 348 patients with absolutely normal dobutamine or dipyridamole stress echo in the contractile response, the major event-free survival curves in a monitoring of 45 ± 21 months were very different in patients with normal CFR (11 events in 282 patients [3.78%]) than with restricted CFR (9/57 [15.78%]), as it may be observed in figures 1 and 2.

In the multivariate logistic regression analysis, CFR was the only indicator of major events (OR 4.03; CI 95% 1.82-8.92; $p = 0.0006$).

We conclude in this work that reduced CFR in patients with normal stress echo due to contractility criteria allowed us to identify a subgroup of patients with worse mid and long-term prognosis, with no differences in relation to the used procedure. (15)

In short, CFR gives us data, easy to calculate and interpret, which complement the information of 2D echo. This improves the communication among cardiologists which may objectively define a physiopathological condition. The most important fact is that both parameters – contractility and coronary flow reserve – should not be used as alternatives or exclusives, but as complements and with additional information during stress echo.

We totally agree with the last European Association of Echocardiography guideline when it emphasizes that CFR assessed by transthoracic echo adds another dimension to stress echo.

The determination of CFR increases test sensitivity and due to its high prognostic value, even with negative tests, according to the classical interpretation criteria, also gives us valuable useful information. That is why we consider that the determination of CFR should be an integral part of pharmacological stress echo.

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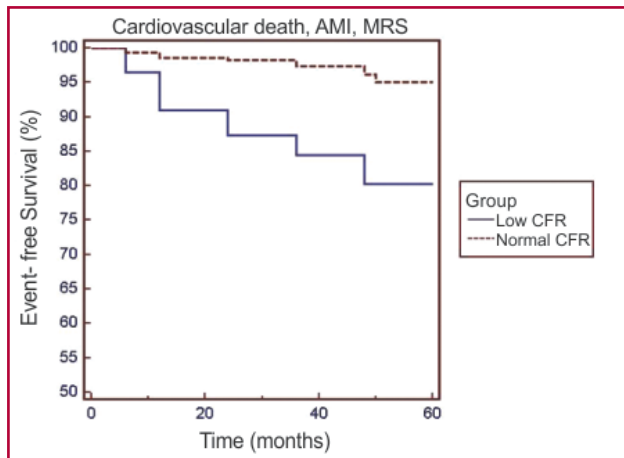


Fig. 1. Kaplan-Meier curves in which, after a monitoring of 45 ± 21 months, the difference in the major event-free survival (cardiovascular death, AMI, MRS) in patients that with a normal stress echo with dobutamine or dipyridamole had a normal CFR or a low CFR simultaneously. AMI: Acute myocardial infarction. MRS: Myocardial revascularization surgery. CFR: Coronary flow reserve.

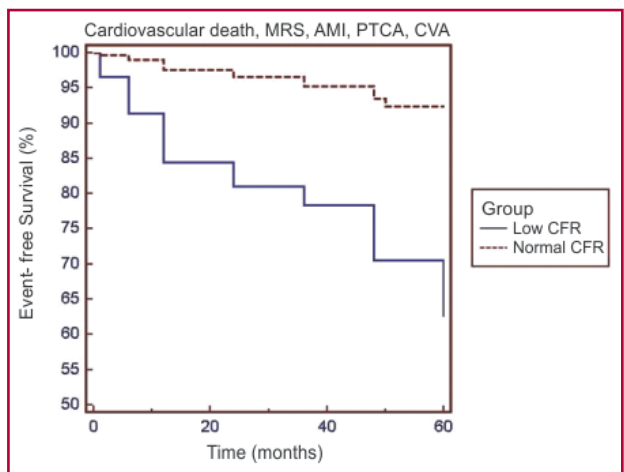


Fig. 2. Curves that belong to the same group of patients in Figure 1 with all the events considered, including CVA and PTCA. The difference in event-free survival curves is even more significant. All patients with normal stress echo with dobutamine or dipyridamole with the classical interpretation criteria. MRS: Myocardial revascularization surgery. AMI: Acute myocardial infarction. PTCA: Percutaneous transluminal coronary angioplasty. CVA: Cerebrovascular accident.

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Conflict of interest statement

The author declares no conflict of interest.

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"The best is the enemy of the good."

POPULAR PROVERB

BACKGROUND

From the timid beginnings, in the world and in our circle, until a solid present and a future with no limits, digital echocardiography with procedures; known as stress echo has suffered a notable evolution.

The Italian Eugenio Picano, one of the pioneers of this technique, reserved a chapter to explain the limited development, the lack of growth in number of studies (or "volume" as we call it nowadays) of this technique, in his first book about this subject. This chapter was called: "Stress-echo: Son of a minor goddess? and he mentioned some difficulties that conspired against a major use of this modality. (1) Some outstanding aspects are still in effect after more than 15 years.

The first inhibiting factor mentioned by Picano was the "psychological" one; subjective and qualitative analysis conspired against the own acceptance of the technique even by echocardiographers.

Other factors were lack of multicentered studies, high occupation of echocardiography laboratories, need of a special training for stress echo and dependence of the acoustic window. Some of them were improved and others were not. For example, the technological advance allows a better image quality. With the advent of second tissue harmonic imaging which was initially designed for contrast echo but used today as part of a routine, and in my opinion obligatory for stress echo the endocardium has been

outstandingly improved with reduction of the number of non-diagnostic studies. Multicentered studies, meta-analysis and agreements have been published and there are specialization courses all around.

However, there are still two matters unsolved with special importance about the topic that concerns us: high occupation of echocardiography laboratories (as Picano says, echocardiography equipments are multipurpose, different from radioisotope studies which are more monovalent) and above all the lack of quantification and objective images for the critical analysis of the results.

Due to the increasing demand of cardiovascular ultrasound studies, the equipment usage time should tend to be reduced more than to be extended. The quantification and subjectivity in the interpretation, cause of several critics related to the interobserver and intraobserver variability, are topics that worry and this is also valid for echocardiography in general, not only for stress echo. In this way, first with tissular Doppler, today with speckle tracking and 3D echo; the goal in stress echo of "numbering things" continues being the search.

THE MEASUREMENT OF CORONARY FLOW RESERVE IN STRESS ECHO

15 years have passed (Gould-1974) from the description of the relationship between the coronary flow reserve (CFR) and the degree of stenosis of epicardial coronary arteries (2) to the first experiences published by the Italian Sabino Iliceto (3) in the measurement of CFR, first through transesophageal echo and then through

transthoracic echo, in this case by Hozumi and his team. (4) In Argentina, the measurement of coronary flow has awakened interest from its onset, both in welfare and research, from one of the pioneers and mentors of stress echo (my Mentor, with capital letter, since he was who awoke my interest in this method), my friend and today my rival in this controversy, Dr. Jorge Lowenstein. (5, 6) His initiative and passion for stress echo and in the last years for the estimation of CFR are worthy of praise and respect.

As it is known, coronary stenosis reduces the capacity of increasing flow with vasodilation. This "coronary flow reserve" may be measured with endovascular Doppler in an invasive way or through transthoracic Doppler.

As the Italian Fausto Rigo states in his excellent revision (2005) entitled "Coronary flow reserve in stress echo: from physiopathological toy to diagnostic tool", the change in flow velocity is measured through the variation of the Doppler sign. (7) From transthoracic echo, the mid-distal flow of the anterior descending coronary artery (AD) may be measured, although the procedure may be carried out in other main coronary arteries with a more laborious technique and with less success.

First, we have to use a high-definition equipment with a good pulsed and color Doppler signal which is not essential for conventional stress echo, where a good definition of 2D echo is required, preferably with second harmonic 2D echo.

A high frequency transducer is also required (5-7 MHz, generally a pediatric one) with a special program which is not the usual for stress echo. When the signal is not ideal, the use of contrast is recommended, at this precise moment not available in our circle. In order to obtain images of parietal motility the transducer should be changed, situation that may be complex in some models, without mentioning his cost.

CFR depends on epicardial arteries and microcirculation. In that way, some pathologies that threaten microcirculation, very frequent in the assessment of patients who underwent stress echo, affect the coronary flow reserve in absence of epicardial coronary artery stenosis. Left ventricular hypertrophy, X syndrome and dilated cardiomyopathy are only some examples. According to Rigo, the measurement of coronary flow reserve should be carried out at the same time the estimate of parietal motility is performed. If the coronary flow reserve is normal and the parietal motility is normal or vice versa, we are in an unsolid ground.

THE ESTIMATION OF CORONARY FLOW RESERVE AS AN INTEGRAL PART OF STRESS ECHO

Beyond these restrictions, the measurement of coronary flow reserve represents a great advance and a qualitative step in the assessment of patients with stress echo. Sensitivity is clearly better in all the series, with a slight loss of specificity. There are objective

records which are easily interpreted. A patient with doubtful data and a moderate obstruction of AD is an excellent candidate for this technique.

The aforementioned does not mean that a systematic way should be used which is the point where this controversy points. At this moment in time, in our circle and around the world, CFR is not an integral part of the study and it is not used as a routine in stress echo laboratories.

The big question is: why has not been spread its use if it is so good? There are several answers for this question (Table 1).

From the different stress echo methods, the vasodilator stimulus with dipyridamole or adenosine is the one that fits in the measurement of coronary flow reserve. Clearly, it is not the best procedure for stress echo, unless it would be used for the perfusion with echocardiographic contrast, as it is used for radioisotope perfusion studies. The heart rate with dipyridamole is not increased and it is better for the measurement of coronary flow reserve. But we should change our usual procedure. The ideal stress for viability and aortic stenosis with low gradient among others with dobutamine may be performed but with more difficulty, that is why it is not a usual indication. In my experience, with exercise is practically impossible. And in our laboratory, as in many laboratories in Argentina and around the world, the exercise is the best procedure in outpatients (80% in our case over 400 monthly studies, 65% in Clínica de Mayo).

For the argentine cardiologist, enthusiast of ergometry, stress echo with exercise as an "imaging ergometry" is very useful. Beyond our enthusiasm with exercise echo from its beginnings, it is curious the fact that even our technicians ("easier and faster") and our patients ("I prefer not being injected") prefer it rather than pharmacological tests, strongly recommended for the measurement of CFR.

Another reason, probably the most important, is that the measurement of CFR is a method for experts. If a special training is required to carry out a stress echo, it is not enough the knowledge about echocardiography; if a special training is required for the measurement of coronary flow reserve, it is not enough to be an expert in stress echo.

In fact, there is only one group in our circle, Dr Lowenstein's, which performed it in a systematic or integral way and that recommends its use. Around the world, publications are also repeated from centers in Italy, Japan, Spain and Argentina. This procedure is not a practice of massive use.

Moreover, the measurement of coronary flow reserve in stress echo is more important for the research than for the clinical practice. If the obstruction is severe, stress echo will surely detect it. If it is not severe, it will probably have a minor clinical significance.

On the other hand, the detection of non-severe

Table 1. Reasons for the “reserves” to measure the coronary flow reserve in stress echo

1. Type of procedure: only vasodilator (dipyridamole or adenosine)
2. Special equipment: high definition Doppler and pediatric transducer
3. Special training and specific experience
4. Laborious and difficult
5. Special examination of the anterior descending coronary artery
6. Abnormal in common pathologies without epicardial coronary obstruction

coronary obstructions may be a double-edged sword. This situation may lead to excessive interventionist behaviors, as angioplasties or unnecessary surgeries.

The estimation of CFR, as a systematic practice, improves the clinical evolution of the patients. Let us imagine, for example, the effects that may have a similar recommendation in the field of public health. With conventional stress echo, we will be more than pleased.

What do guidelines say about the measurement of CFR? The European consensus defends the technique as an integral part of stress echo, due to its major sensitivity and mild minor specificity. (8) This technique should not be used as an only parameter (it should be always considered with parietal anomalies) and it should be used by expert hands with appropriate equipment and always with vasodilators. Curiously, the American Society of Echocardiography guideline recommendations for stress echo do not mention the estimation of coronary flow reserve. (9) All a definition in itself.

CONCLUSIONS

The measurement of CFR during stress echo is a technique that improves sensitivity in the detection of significant obstructions of the anterior descending coronary artery. The procedure is only recommended for obstructions in this location and there is only an experience for the procedure with vasodilators which is not the usual for this technique. It is feasible but it requires special equipment and specific training.

For some cases, it may be useful, but its systematic use may not be recommended as an integral part of stress echo.

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AGONIST'S REPLY

Undoubtedly, perfection does not exist, the search of the Holy Grail is a frustrating and unattainable task; however, the need of looking for better results is the engine that makes us advance and grow.

For this reason, we believe that the visualization of coronary arteries and the determination of its reserve during all pharmacological studies (dipyridamole and dobutamine) are a real progress in the evolution of stress echo.

This technique is not any more the daughter of a minor goddess, as Eugenio Picano asked himself; on the contrary, every time it looks more like Artemis (twin sister of Apollo and daughter of Zeus) that with her 20 breasts represents, nowadays, all the possibilities that this method has and, possibly, the knowledge of CFR is the one of major diagnostic and prognostic impact.

If the fact that there is no mention in the American Society of Echocardiography guidelines calls your attention, I remind you that: 1) in the USA, studies are performed by technicians that do not have any experience, due to cardiologists do not teach them, 2) doctors think that in obese patients, the procedure is not feasible when Takeuchi showed in Chicago that except for rare exceptions, the AD coronary artery is always visible, 3) doctors think that the procedure may be only carried out with dipyridamole when its feasibility with dobutamine was also shown, 4) doctors do not accept to prolong a study, when actually, we are talking about 5 additional minutes well-invested and

5) the most important reason, they do not perform it due to it is not recognized as a practice with economic reward.

As regards Table 1, Reasons for the “reserves” to measure the coronary flow reserve in stress echo”, we have already crossed several bounds and nowadays the measurement of CFR with dipyridamole in the three arterial territories and with dobutamine in the AD is feasible; with the new matrix transducers we do not use the pediatric ones any more and nothing is laborious and difficult if it is carried out as a routine.

Dr. Jorge Lowenstein

AGONIST'S REPLY

As it happens in any controversy, the extreme positions of both “opponents” finally coincide. This case is not an exception.

I agree with the agonist's arguments, Dr. Lowenstein, with the major spreading of exercise echo and the preference of dobutamine echo among pharmacological tests. Exercise echo is faster, better and, besides, cheaper. The images obtained in a patient in rest and with no increase of the heart rate make dipyridamole echo more important as regards imaging quality. But most of the persons that do stress echo began with dipyridamole and then with dobutamine or exercise, according to preferences. In order to determine CFR, we have to use again dipyridamole, something that we have almost forgotten. But, moreover, the assessment of CFR is technically more demanding than exercise echo.

All in all, stress echo with dipyridamole with measurement of CFR is an alternative to procedures with exercise and dobutamine.

I also agree in the need of registers and objective data. The measurement of CFR is an advance in this sense, but it has the aforementioned difficulties, and also coincident, when studying other territories beyond the anterior face. We may add to the aforementioned, alterations of CFR which are frequent in the clinical practice due to other causes apart from the obstruction of epicardial coronary arteries.

As a result, the measurement of CFR is not popular among people that perform stress echo, in our circle and around the world. Interventionist cardiologists got excited about this practice but they finally gave it up.

I congratulate Dr. Jorge Lowenstein for his excellent results in his laboratory which guarantee his skill and dedication easily recognized. However, I think that he will not reach his goal of imposing the determination of CFR as an integral part of stress echo out of him. Not everyone has last generation equipment with multifrequency matrix transducers that allow the identification of coronary color flow with no need of changing it.

Anyway, I think that stress echo laboratories should have specialized professionals to carry out the measurement of CFR in special cases. Probably, the reappearance of echographic contrast will add new ideas to continue improving stress echo and getting over the limitations. The best way to improve the technique is to be critical.

Dr. Marcelo Trivi