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Role of echocardiography in risk stratification and treatment decision-making

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Dr. Pieroni:
Multimodality imaging plays a central role in the management of hypertrophic cardiomyopathy, from diagnosis to treatment and sudden cardiac death stratification. Echocardiography in particular is important to establish a diagnosis, determine the pattern and the degree of hypertrophy, and mostly to establish the presence and the severity of LVOT obstruction. We can say that echocardiography together with magnetic resonance imaging, in most cases allow to establish a likely diagnosis in a patient with an hypertrophic phenotype before the confirmation by genetic testing or additional tools.

From a clinical point of view, we now know that sudden death is not the main clinical feature of hypertrophic cardiomyopathy, while obstruction and heart failure are the more common clinical profile. Left ventricular outflow tract obstruction is present in up to 40% of patients at rest, but may be provoked in an additional 30% of cases by exercise echocardiography, as you can see in this picture. In the recent guidelines, it's class I recommendation to perform an exercise stress echocardiogram in all those patients who are symptomatic but don't have a gradient at rest. In those patients who are highly symptomatic and we cannot detect a gradient by stress echocardiography, it may be important to repeat the test after lunch, particularly after a lunch rich in carbohydrates, because this may unveil a gradient in these patients.

Identification of obstruction is particularly important because now we have specific drugs that may treat obstructive patients. Myosin inhibitors have been introduced in the recent European and American guidelines with a Class IIa and a Class I indication. The story of myosin inhibitors starts with the discovery that in human myocardium, myosin may present in different states, very engaged states where myosin heads are engaged with actin filament, and at the opposite, a super relaxed state. We also know now that in hypertrophic cardiomyopathy, there is a lower prevalence of super relaxed myosin with an higher prevalence of activated myosin engaged with the actin filament. Myosin modulators, in this case mavacamten and aficamten, may increase the number of myosin heads in the super relaxed states. At the opposite, Omecamtiv that may have an application in dilated cardiomyopathy, may increase the interaction and the power stroke of myosin in dilated cardiomyopathy.

The mechanism of action of mavacamten is to reduce the number of myosin actin cross bridges and to decrease the excessive contractility that we have in patients with hypertrophic cardiomyopathy.

This is an example of the mechanism of mavacamten. This is a well with myosin motor fixed to the well. What you can see is actin molecules that are moved by the myosin heads. In the left, there is the control, the normal myocardium in hypertrophic cardiomyopathy. On the right, the same molecule with mavacamten. You see that the actin, the intensity, and the velocity of actin movements are highly reduced. Starting from basic science and clinical studies, we identified a molecular target and a small molecule targeting this molecular target. Then we have preclinical data and clinical trials leading in the last years to the approval of the first myosin inhibitors, that is

mavacamten.

In the EXPLORER trial, patients were randomized to placebo or mavacamten. You can see that in the mavacamten arm, a higher number of patients met the primary endpoint. It means an increase, peak oxygen uptake, or an improvement of the NYHA class. This was due mainly to a significant reduction of the left ventricular outflow tract gradient either at rest or after provocation without affecting left ventricular ejection fraction. This was paralleled by a significant reduction of biomarkers, namely NT-proBNP and mostly troponin. This may suggest that behind the hemodynamic consequences, this drug may also influence the biology of myocardial cells.

Now we have long-term data from the EXPLORER-HCM trial and we can say that the effect of the drugs are consistent over time. We have an established reduction of the gradient, either at rest or provoked, and a sustained reduction of NT-proBNP. We have also a signal for an improvement of diastolic function, a reduction of left arterial volume, and an improvement of the diastolic function.

The next trial was VALOR-HCM, enrolling patients with a gradient higher than 50 millimeters of mercury and NYHA Class III-IV, candidates for septal reduction therapy. The patients were randomized to placebo or mavacamten, and after 16 weeks, patients in placebo cross over to the treatment group. What we observed here is that at week 16, 82% of patients treated with mavacamten were no longer eligible for septal reduction therapies. After 56 weeks, 91% in the original treatment group and 81% in the switched group were non-eligible to septal reduction therapy. This was mainly due to a reduction in the gradient and also to an improvement of the NYHA class, as you can see here, at 16 and 56 weeks.

Similar findings were obtained with another molecule, aficamten, similar results in terms of gradient reduction and NYHA class improvement. This is the Phase 3 study, SEQUOIA trial published in New England Journal of Medicine, showing an improvement of oxygen uptake, reduction in the gradient, improvement of NYHA class, and in the Kansas City quality of life questionnaire.

Based on these trials, European guidelines and American guidelines introduced the myosin inhibitors for all those patients still symptomatic despite the treatment with beta-blockers or calcium channel blockers. This was in Class IIa in the European guidelines based on the EXPLORER-HCM trial and in Class I in the American guidelines based on both trials.

This is an example of a patient treated with mavacamten. This is a male, 45-year-old with obstructive hypertrophic cardiomyopathy who entered the early access program in February 2024. You see here the echocardiographic features with a gradient of 65 millimeter at rest increasing to 81 millimeter of mercury with Valsalva and an impaired diastolic function. This is the baseline just on nadolol. You see the obstruction and the 65-millimeter gradient. This is the same patient with nadolol plus mavacamten. There is a relief of the obstruction and a reduction of the gradient. This is the same for the Valsalva gradient, 81, and then 10 millimeters of mercury. In these patients, we also observed an improvement of the diastolic function. You see with nadolol a triphasic pattern suggesting a severely impaired diastolic function and a normalized diastolic function with mavacamten on top of nadolol.

Regarding the sudden cardiac death risk stratification, we know that in the European guidelines, we use the sudden death risk calculator, including clinical and echocardiographic variables, while in the American guidelines, we have the risk core approach to the sudden death risk stratification. Which one of the approach is better, we don't know, but in this paper, based on the SHARE registry, the authors compare the US approach with the non-US approach, and they observed that in the US, there is a twofold higher ICD implantation leading to a lower burden of risk factors in the US patients compared to the European patients. What we had during the follow-up is that we had a higher number of appropriate shocks in the non-US cohort compared to the US cohort and in patients not receiving the ICD, there were a similar number of sudden death that were not prevented. This study suggested that the European approach currently is to be preferred in these patients.

In the most recent risk stratification flow chart, additional parameters were included, like the extension of scar and the presence of ventricular aneurysm. Echocardiography is important to detect apical aneurysm even when in some cases we can add the contrast agent to visualize the apex. CMR in some cases may be important to visualize the scar and also to visualize thrombi in the apex. An aneurysm larger than two centimeters may increase the risk of sudden death and the risk of thromboembolic events. This is an example of the apical aneurysm with extensive fibrosis due to myocardial ischemia. We can say that with echocardiography and CMR, we can really imaging the arrhythmic risk.

The next question is, will myosin inhibitors modify the arrhythmic risk in this patient? We don't know. There are not enough data, but there are some hints for the trials. This is a patient. Just look at the ECG. Following the introduction of mavacamten, there is a normalization of the repolarization together with the disappearance of the gradient. This is a very recent paper from our group showing that together with mechanical resynchronization shown by GLS and peak systolic dispersion, there is also an improvement in QT dispersion suggesting that likely these molecules will also modify the arrhythmic risk in these patients.

This is my last slide, and in this picture, you can see the progress that we had in the management of hypertrophic cardiomyopathy since

the first description in 1958 through ICD development, septal reduction therapies, and now myosin inhibitors. We are now really more and more able to treat this disorder.

Thank you for your attention.

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