What Is the Relevance of an Intraventricular Ejection Pressure Gradient Induced by Exercise?

Raquel Yotti

Servicio de Cardiología, Hospital General Universitario Gregorio Marañón, Madrid, Spain.

Pressure gradients in the left ventricle (LV) during ejection have traditionally been considered a pathological finding. For more than 20 years, however, systolic intraventricular pressure gradients (IVPGs) have been known to exist in physiologic form in normal subjects. Using high-fidelity micromanometers, pressure differences of 3 to 5 mm Hg between the apex and the left ventricular outflow tract (LVOT) have been measured in the normal heart at rest. These pressure differences are the result of an acceleration of blood due to myocardial contraction (initial ventricular impulse)[1] and of physiologic disproportion between the chamber diameter and the LVOT (ventriculoannular disproportion).[2] These physiologic IVPGs have been empirically shown to be closely related to left ventricular systolic function.[2-4]

In response to inotropic challenge induced by beta-adrenergic drugs or physical exercise, physiologic IVPGs increase noticeably. Nevertheless, there are few data on the potential extent of this physiologic response. In experimental animals with a structurally normal heart, the mean IVPG induced by beta-adrenergic drugs is about 15 mm Hg, although IVPGs above 80 mm Hg have been reported.[3] In humans, the extent of systolic IVPGs in asymptomatic subjects at rest versus in stress situations has not been assessed using echocardiography. In 1 study with 6 healthy volunteers who underwent cardiac catheterization, IVPGs above 15 mm Hg were recorded during sub-maximal exercise.[2] Similarly, in a recent echocardiography study performed with healthy volunteers, we found IVPGs above 12 mm Hg during the administration of low doses of dobutamine (maximum 10 µg/kg/min).[5] The possibility that higher IVPGs could develop physiologically in response to greater effort or more powerful inotropic stimuli is not clear, however.

In the absence of a normal pattern, it may be difficult to establish the pathophysiologic role of IVPGs observed in patients who undergo stress echocardiography or dobutamine stress testing. The study by Cabrera et al published in this issue of REVISTA ESPAÑOLA DE CARDIOLOGÍA contributes to the limited evidence that is currently available. These authors used Doppler echocardiography to analyze the IVPG in the immediate post-exercise period among 134 patients with chest pain and exertional dyspnea. Eighteen (13%) of these patients were found to have pathological IVPGs, defined as the presence of systolic flow with a maximum velocity equal to or higher than 2.5 m/s and dagger-shaped late peaking in the LVOT or mid-ventricular region.[6] The results of this study provide valuable information and raise new questions about the pathophysiology, diagnosis and clinical and therapeutic implications of exercise-induced IVPGs.

PATHOPHYSIOLOGY

Parallel to the traditional debate about the hemodynamic role of obstruction in patients with hypertrophic cardiomyopathy,[7] 3 types of potential mechanisms implicated in the development of exercise-induced IVPGs can be proposed: *a)* mid-systolic obstruction due to systolic anterior motion (SAM) of the mitral valve with restriction of ejection flow; *b)* end-systolic obstruction secondary to ventricular cavitary obliteration; and *c)* augmentation of physiologic non-obstructive IVPGs. These mechanisms should be interpreted as a whole, and they can be present in combination in various situations.

Correspondence: Dra. R. Yotti.
Laboratorio de Ecocardiografía. Servicio de Cardiología. Hospital General Universitario Gregorio Marañón.
Dr. Esquerdo, 46. 28007 Madrid. España.
E-mail: ryotti@mi.madritel.es

Exercise-induced SAM of the mitral valve has been implicated in the development of IVPGs, although its incidence varies among the published series. In one study, echocardiographic study disclosed mitral valve SAM in most patients (68%) with exercise-induced IVPG.[8] However, the study done by Cabrera et al. described this mechanism in only one patients with inducible IVPGs (5%). When interpreting these differences, it should be taken into account that the first series did not exclude non-hypertensive patients with ventricular hypertrophy and possible hypertrophic cardiomyopathy and that 21% of these patients were found to have SAM in the baseline echocardiogram. Exercise-induced SAM of the mitral valve has traditionally been attributed to the Venturi effect, but recent echocardiographic data suggest that it is initiated by the flow drag that actively pushes the anterior leaflet toward the septum.[9] This effect is enhanced when the acceleration of blood increases in response to inotropic stimuli. For SAM to occur, however, the ventricular chamber and the mitral valve must have a specific geometry. This predisposing geometry is normally found in patients with hypertrophic cardiomyopathy, as well as some patients who have undergone surgical repair of the mitral valve. In elderly patients with basal septal hypertrophy, SAM of the mitral valve has also been described as a mechanism of dobutamine-induced IVPGs.[10]

Secondly, the increase in ventricular emptying induced by myocardial hypercontractility can enhance cavitary obliteration, leading to end-systole mid-ventricular pressure gradient obstruction, when virtually all stroke volume has already been expelled. In these patients, ventricular obstruction is the result of above-normal ventricular emptying, and not limited ventricular emptying. This is the mechanism most often implicated in IVPGs observed during dobutamine stress testing.[11] Hypertrophy enhances this type of obstruction; however, ventricular cavitary obliteration caused by interventions that modify the loading conditions, such as amyl nitrite administration or Valsalva maneuvers, has also been reported in normal subjects without left ventricular hypertrophy or hypercontractile conditions.[12]

Lastly, it is possible for the physiologic phenomenon described at the start to be enhanced, with IVPGs present in the normal heart increasing with exercise. This mechanism could be particularly relevant in patients with relatively low maximum velocities, which reflect a lower degree of obstruction. In the study by Cabrera et al, most of the patients with IVPG did not develop symptoms with exercise, but interestingly, these patients had lower velocities (2.37±0.77 m/s) than those who did present symptoms. These data suggest the possibility that the IVPGs observed in the group of patients with relati-

vely low velocities could be the result of a different pathophysiologic mechanism, in which obstruction plays a minor role. From the theoretical point of view, the induction of a hyperdynamic response in a ventricle with a greater ventriculoannular disproportion could produce an increase in non-obstructive physiologic IVPGs. In this context, Cabrera's identification of LVOT diameter indexed by body surface as the only independent predictive factor for the development of exercise-induced IVPGs has special pathophysiologic relevance. Although the disproportion between the cross-sectional area of the ventricular chamber and the LVOT was not directly measured, it is reasonable to assume that patients with a small LVOT relative to their body surface area may also have a larger ventriculoannular disproportion, and therefore higher IVPGs. This finding has not been described previously, but could explain why patients who developed IVPGs with exercise had significantly higher maximum aortic velocities at baseline than those that did not. Finally, the presence of an excessive decrease in peripheral vascular resistances, in line with the well-known competitiveness between the extrinsic and intrinsic components of total ventricular systolic load,[2] could also enhance this physiologic phenomenon and lead to abnormally high non-obstructive IVPGs.

DIAGNOSIS

Pressure gradients are usually calculated by echocardiographic study using the blood velocity in the simplified Bernoulli equation ($4v^2$). However, this approach is valid only when the following is true: *a)* there is an anatomic obstruction; *b)* the velocity proximal to this velocity is negligible with respect to the distal velocity; and *c)* the inertial acceleration of the blood is low with respect to the convective acceleration. Estimation of pressure gradients in the absence of obstruction (or in the presence of lower degrees of obstruction) requires the use of the complete form of the Bernoulli equation or the Euler equation. Our group recently developed a new method based on post-processing of Doppler echocardiography images that can be used to solve the Euler equation and accurately measure the IVPGs in the absence of obstruction.[5,13]

In the particular case of exercise-induced IVPGs, use of the simplified Bernoulli equation is reasonable, as long as the mechanism presumably implicated is ventricular obstruction and the velocity distal to the obstruction is sufficiently high. Normally the error made using this simplified approach is considered negligible when the proximal velocity is below 1.5 m/s and the distal velocity is above 2.5 m/s. Nevertheless, any rigid cutoff point used in physiology tends to have limitations.

CLINICAL AND THERAPEUTIC IMPLICATIONS

Dobutamine-induced IVPGs have been causally related to the presence of angina and exertional dyspnea.[10] This assertion is still speculative, however, and has been refuted by some authors.[11] The clinical significance of IVPGs induced by physical exercise raises even more questions. The various series have been unable to reproduce dobutamine-induced IVPGs in response to exercise.[11] This fact may be directly related to the differing effects of dobutamine and exercise on contractility and loading conditions. Dobutamine produces a greater increase in myocardial contractility and a greater decrease in peripheral resistances, and consequently can cause higher IVPGs. Moreover, although preload is decreased more by dobutamine than supine exercise,[14] exercise in the standing position inherently leads to an additional decrease in preload that fosters the development of IVPGs. This can mean that IVPGs measured in supine position during the immediate post-exercise period are lower than those induced during normal physical activity while standing.

In any case, we may conclude that the potential clinical repercussions consequences of exercise-induced IVPGs cannot be analyzed from information derived from pharmacological challenge tests, and therefore studies specifically designed for this purpose should be conducted. The study performed by Cabrera et al. adds valuable information as it analyzes both the incidence of this phenomenon as well as factors related to its appearance and the clinical progress of patients who present it. In this series, the percentage of patients with a systolic flow velocity during exertion equal to or higher than 2.5 m/s is noticeably higher than that reported earlier. Nevertheless, these increased velocities were accompanied by symptoms in only a few patients and were not associated with adverse events in the follow-up. Although the 5 patients from this group who presented symptoms had higher IVPGs, the authors acknowledge that the study data do not allow a definitive causal relationship to be established between exercise-induced IVPG and the appearance of symptoms.

As a result, there is unfortunately no evidence on the therapeutic approach that should be taken in these patients and only a mechanical approach can be suggested. The hemodynamic significance of a pressure gradient with regard to limitation on ventricular emptying will depend on the presence of obstruction, on the anatomic site of such obstruction and on the time of systole at which it occurs. In the group of patients with IVPGs induced by SAM of the mitral valve, the clinical implications could be similar to those of hypertrophic cardiomyopathy with provocable obstruction. Therefore, a causal relationship between the appearance of IVPGs and the induction of symptoms is more likely to be found in this subgroup. As in hypertrophic cardiomyopathy, negative inotropic drugs could play a therapeutic role. In contrast, when the mechanism of IVPG is ventricular cavitary obliteration, its clinical significance may be different. Because obliteration occurs when almost the entire ejection volume has been expelled, any anatomic obstruction induced does not affect ventricular emptying, and therefore the hemodynamic consequences usually found with systolic flow limitation cannot be presumed to exist. Nevertheless, although IVPGs secondary to this mechanism might not have any inherent hemodynamic or clinical consequences, they could be used as a diagnostic marker to identify a group of patients with ventricular hypertrophy or insufficient preload in which ventricular filling is compromised. In this case, treatment should target the underlying condition. In Cabrera's study, patients found to have an exercise-induced IVPG were more likely to be receiving diuretic therapy. The presence of cavitary obliteration with exercise could be sufficient cause to discontinue or reduce this therapy in order to prevent volume depletion. Lastly, when the mechanism implicated is predominantly non-obstructive (more probable in relatively low IVPGs), the IVPGs may be related to the enhancement of a physiologic phenomenon, and therefore cannot be expected to produce cardiovascular symptoms or to require medical treatment or follow-up.

Another interesting question raised by this article is whether or not stress testing should be supplemented with Doppler echocardiography to identify and treat any potential source of symptoms. Echocardiographic study may allow detection of abnormally high systolic velocities and, more importantly, the mechanism that leads to such velocities (e.g., SAM of the mitral valve or cavitary obliteration). A potentially reasonable compromise would consist of stress echocardiography to supplement conventional ergometry, at least when the resting echocardiogram indicates that the patient may be more likely to present dynamic intraventricular obstruction.

In conclusion, small non-obstructive IVPGs that increase during physical exercise always exist under normal conditions. This physiologic response may play an important pathophysiologic role in inducing abnormally high exercise-related IVPGs. Differentiation between the obstructive and non-obstructive mechanisms potentially involved in the development of exercise-induced dynamic pressure gradients could have relevant diagnostic and therapeutic implications.

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