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*Artículo:*

# Exit pathway of the left ventricle. Clinical aspects. From praxis to rationale

# *Exit pathway of the left ventricle. Clinical aspects. From praxis to rationale*

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## Summary

Aspects of subaortic stenosis are described, using as a basis, the clinical spectrum of hypertrophic cardiomyopathy and discrete subaortic stenosis. The anatomy, pathology, clinical presentation, diagnosis, treatment and outcomes for each are summarized. A comparison of outcomes and knowledge gaps between the two conditions is discussed.

## Resumen

SALIDA DE VENTRÍCULO IZQUIERDO. ASPECTOS CLÍNICOS. DE LA PRAXIS A LO RACIONAL.

Se describen aspectos de la estenosis subaórtica, utilizando como base el espectro clínico de la cardiomiopatía hipertrófica y de la estenosis subaórtica discreta. Se resumen la anatomía, patología, presentación clínica, diagnóstico, tratamiento y hallazgos. Se discute una comparación entre los hallazgos y el conocimiento faltante entre las dos condiciones.

**Key words:** Subaortic stenosis. Hypertrophic cardiomyopathy. Discrete subaortic stenosis.
**Palabras clave:** Estenosis subaórtica. Cardiomiopatía hipertrófica. Estenosis subaórtica discreta.

The outflow of the left ventricle may be in a morphologically right or left ventricle and to either a pulmonary or aortic great artery. For purposes of this paper, discussion will be limited to the morphologic left ventricle, which empties to the aorta. The exit pathway of the left ventricle may be disturbed through obstruction or abnormal valve function and obstruction may be at the sub-, valvar or supravalvar level. Again, for clarity and brevity, the discussion will be limited to obstruction at the subvalvar level, and further limited to discussion of obstructive hypertrophic cardiomyopathy and discrete subaortic stenosis.

## Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is now understood to be a genetic cardiac disease with heterogeneous phenotypic expression and prognosis occurring in a frequency of at least 1:500 *(Table I)* in the general population.[1,2] It is unique because it may present at any stage of life, and because of its natural history is highly variable, resulting in some patients with normal longevity and others who die suddenly. Overall, the annual mortality among HCM patients is approximately 1%; it is the most common cause of sudden death in young athletes.

### Pathology

The proximity of the aortic valve to the mitral valve creates a tunnel-like exit path for the left ventricle, which in turn creates the substrate for anterior displacement of the anterior leaflet of the mitral valve in situations where the velocity of emptying is increased in the outflow tract. Hypertrophy of the left ventricle and in particular, hypertrophy of the interventricular septum decreases the caliber of the left ventricular outflow tract creating a self-perpetuating cycle of hypertrophy and increasing stenosis. Left ventricular hypertrophy may be diffusely distributed or only mild wall thickening, localized to a single segment. The hypertrophy is typically, but not always, asymmetric, and only 25% of patients have obstruction. Histologically, the ventricular myocardium is disorganized, composed of hypertrophied myocytes with variable, bizarre shapes and multiple intercellular connections often



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arranged in chaotic array and laced with abnormal intramural coronary arteries, likely accounting for compromised myocardial reserve and ischemia.[1] HCM is considered to be a disease of the sarcomere and is inherited as a Mendelian autosomal dominant trait caused by mutations in any one of 10 genes which code for various sarcomeric proteins. Genotype-phenotype studies have demonstrated incomplete penetrance and highly variable clinical courses even within a single family cohort, with the same molecular genetic defect.[2,3]

### Clinical presentation

Up to 25% of patients with HCM reach normal life expectancy with mild or no disability and without major therapeutic interventions. Others have lives interrupted by adverse clinical events, ranging from sudden unexpected death, embolic stroke or heart failure.[2] Dyspnea, angina, and presyncope and/or syncope on exertion are typical of patients with obstructive HCM, but the severity of symptoms on upright exertion do not necessarily correlate with the magnitude of obstruction (which is often measured in the supine position).[3] Congestive heart failure may occur with severe obstruction or in the presence of severe ventricular dysfunction, especially in the presence of atrial fibrillation.

### Diagnosis

The most definitive method for establishing the diagnosis of HCM is laboratory DNA analysis for mutant genes. Molecular genetic testing, however, is still currently available only in research centers. Clinical diagnosis is by echocardiography, and increasingly by magnetic resonance imaging, though a detailed and accurate family history become extremely important given the disease's autosomal dominant genetic basis. When a DNA-based diagnosis is not feasible, it is recommended that family members be screened including history, physical examination, 12-lead ECG, and echocardiography at annual evaluations during adolescence and about every five years thereafter.[2]

### Treatment

Therapy of HCM depends on both family history and on the assessment of risk of sudden cardiac death, which, in turn depends on left ventricular pathology and function, and the presence or absence of symptoms, including arrhythmias. The overall probability of death has been shown to be greater among patients with outflow obstruction than among those without obstruction, but the likelihood of severe symptoms and death related to outflow tract obstruction did not increase as the gradient increased.[4] Beta blockers or calcium channel blockers may relieve symptoms in some patients, while others remain severely symptomatic despite maximal optimal medical therapy. Septal myectomy reduces or abolishes left ventricular outflow tract gradients in HCM and may provide long-lasting symptomatic improvement.[5] In recent years, alcohol septal ablation has been found to be equally effective in reducing obstruction and subjective exercise limitation in appropriately selected patients.[6] Other options for treatment include pacemaker insertion, and mitral valve replacement.

## Discrete subaortic stenosis

Fixed subaortic stenosis (SAS) may be divided into discrete and tunnel forms, with the former being more common.[7] Approximately one-half of cases of discrete subaortic stenosis occur in isolation and it appears to be acquired as it does not appear embryologically, is rarely reported in neonates, and has been reported after previous documentation of a "normal" left ventricular exit. Discrete subaortic stenosis accounts for 8-10% of all cases of left ventricular outflow obstruction in children, although it is recognized to occur in adults with a prevalence of 6.5% of all adults with congenital heart disease, admittedly a selected sample.[8] As with aortic valve disease, a higher incidence of SAS is reported in males, and a genetic influence is suggested but not proven, by familial cases.

### Pathology

Discrete subaortic stenosis consists of a thin diaphragm or fibrous ridge alone or in association with a muscular base located below the aortic valve. The obstruction is thought to be progressive over time with resultant left ventricular hypertrophy, dysfunction and/or aortic regurgitation secondary to thickened and distorted aortic valve leaflets from the subaortic jet. This damage may increase the likelihood of infective endocarditis on the valve or membrane.

### Clinical presentation

The majority of cases of SAS is asymptomatic and is often detected by a prominent murmur, or

**Table I.**

| | HCM | Discrete SAS |
|---|---|---|
| Prevalence | 0.2% (~1:500) | 3-10% CHD (0.1%) |
| Genetics | Autosomal dominant | Unknown |
| Population affected | All ages (rare in infancy) | All ages (rare in infancy) |
| Pathology | Subaortic obstruction 2º to ASH, SAM<br>Cardiomyocyte disarray | Membranous subaortic diaphragm with without fibrous base. Myocardium normal. |
| Diagnosis | Molecular (preferred but not available). Echo/MRI | Echo/MRI/Catheterization |
| Treatment | Symptomatic obstruction: medical, surgical or alcohol ablation or ICD | Surgical |
| Outcome | SCD unrelated to Rx | Recurrence aortic regurgitation |

diagnostic testing. Symptomatic patients are often those with higher outflow tract gradients and typically demonstrate dyspnea, chest pain, and/or syncope. Typically the murmur of subaortic stenosis is a left ventricular harsh outflow murmur without the telltale ejection click found in valvar aortic stenosis.

### Diagnosis

Diagnosis is usually via echocardiographic workup of a presenting murmur, though both cardiac catheterization and magnetic resonance imaging may delineate SAS. Unlike HCM, the electrocardiogram in SAS is only abnormal in those patients with significant stenosis or associated cardiac lesions.

### Treatment

Treatment is usually surgical, but with a substantial recurrence rate of 7-27%, especially so in younger children.[9] Membranectomy with or without myotomy or myectomy is the accepted method but there are still uncertainties concerning indications for and timing of surgery, and operative methods. The major concern has to do with the progression of aortic regurgitation, with some centers recommending early surgical excision to alleviate even mild degrees of obstruction to the left ventricle and reduce the potential damage to the aortic valve that may result in aortic regurgitation. Others cite the slow progression of obstruction and recommend surgery only if aortic regurgitation develops or becomes significant. Freedom has not demonstrated a reduction in the recurrence rates after early surgery.[10] Hanley and colleagues, however, have demonstrated that "an aggressive surgical approach to discrete SAS produces excellent relief of obstruction and frees the valve leaflets, significantly reducing associated aortic regurgitation at early and mid-term follow-up with low morbidity for primary operation".[11] We have identified that those patients having more rapid progression of the subaortic gradient are more likely to have surgery and to have recurrences.

## Comparison

### Knowledge Gaps

Both obstructive HCM and discrete SAS are complex forms of left ventricular egress abnormalities and both occur throughout the lifespan of humans. We diagnose both primarily with echocardiography, with due consideration given to family history and symptomatology. Our treatments for both classes of abnormalities are relatively gross attempts at alleviating disabling symptoms and preventing further progression.

Although great strides have been made in the understanding of the genetic mechanisms underlying HCM, the complexity of the genetic abnormalities and their expression in phenotype leave us with an inability, with certainty, to diagnose, or prognosticate in patients with HCM. Our treatments are still attempts at alleviating symptoms rather than curing the disease. With discrete SAS, we have even less genetic understanding of the abnormality, but have approached the treatment in a similar manner: alleviate symptoms if present, and prevent progression, if possible. Controversies in management of both these diseases are related to our incomplete understanding of the pathology, genetics and complex pathophysiology of the vastly variable human response to minute mutant changes in DNA. As treatments become more expensive and our molecular genetic diagnostic screening identifies increasing numbers of asymptomatic people at risk, are we approaching this challenge in the most rational way which would lead to the greatest good for the greatest number?



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