Hypertrophic cardiomyopathy

Characterization and treatments for one of the diseases that more deaths generates

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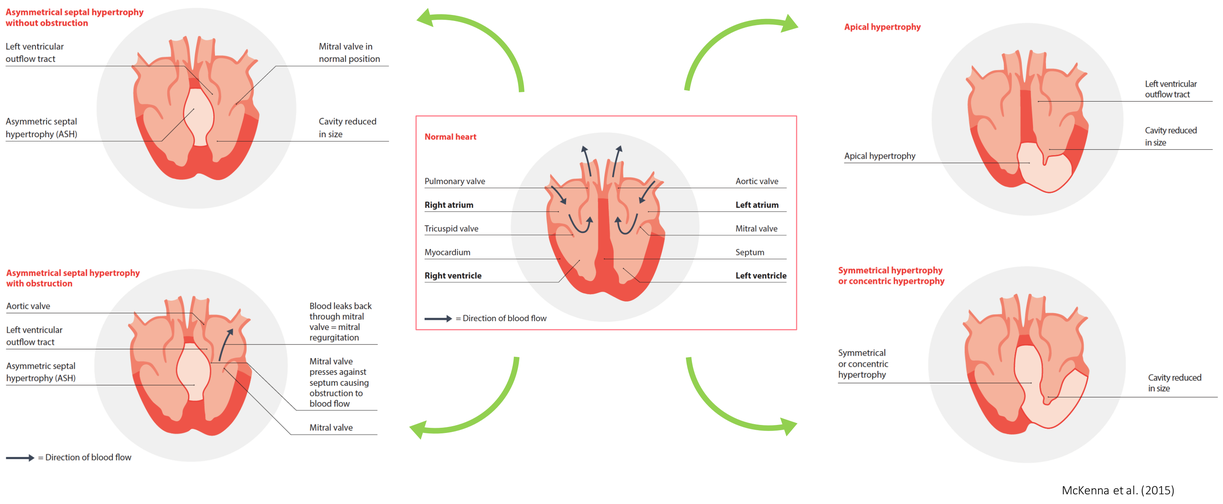
Introduction

Hypertrophic cardiomyopathy (HCM) is one of the most common heart diseases that affect people (1:500). Despite being a dominant autosomal disease, it has different degrees of severity because the phenotype expression depends on many factors, some of which are still not completely clear. Individuals with the same genotype may present different phenotypes, from not presenting any symptoms to a sudden death. The disease can be initially silenced and manifested over time and can affect from young athletes to adults. Because it concerns so many people and it's often difficult to diagnose, scientists are interested in finding new techniques to detect the disease more prematurely and also develop more effective treatments to avoid the most serious symptoms.

HCM is a structural and functional alteration of the myocardium, the muscle responsible for the heart contraction. Due to mutations in several genes that encode for sarcomere proteins, the left ventricular wall manifests **cell disorder**, **fibrosis**, **rigidity**, **hyperdynamic contraction** and **diastolic dysfunction**, causing its thickening. Because the blood volume to be pumped is smaller for that reason, not enough oxygenated blood is available throughout the body.

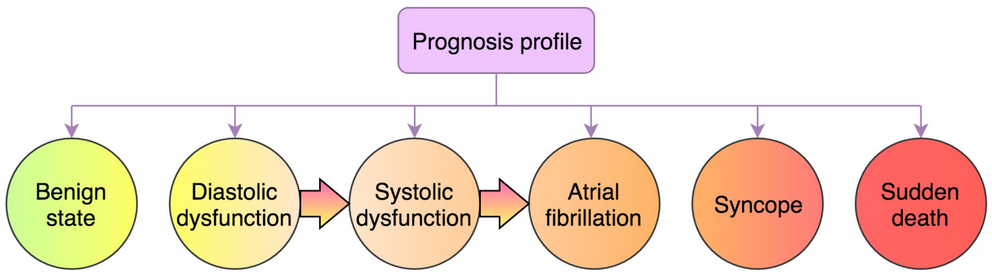


McKenna et al. (2015)

Course of the disease

The disease can develop in different ways because of different factors:

- **Allelic imbalance**: One of the alleles is more expressed than the other and, if it is also mutated, produces a mosaicism in the tissue that does not maintain its proper functioning.
- **Epigenetics**: These are all the cellular mechanisms that regulate genes expression (methylation, acetylation, phosphorylation, etc.). If those modify the promoter regions of the mutated genes, it can be stimulated the manifestation of hypertrophy.
- **Other risk factors**: Gender, blood pressure and physical activity.



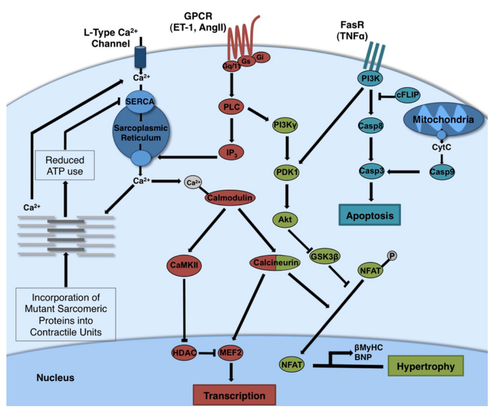
Modified from Pérez Riera et al. (2015)

The main perceivable symptoms of MCH can be identified with the acronym "SAD"

- **S**yncope and **S**udden death
- **A**ngina
- **D**yspnea

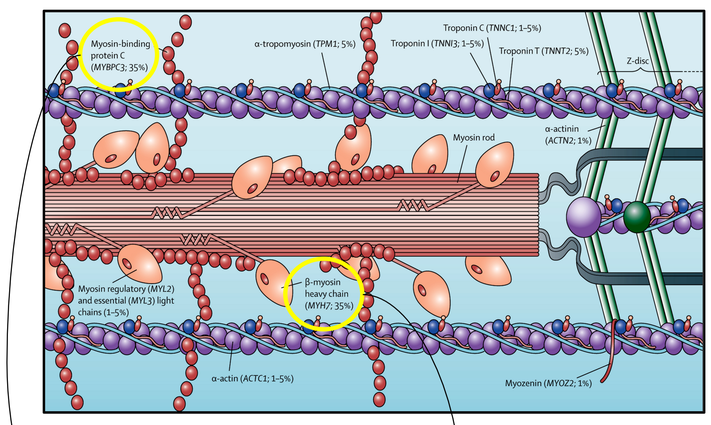
Signaling pathways of hypertrophy

Against a stress, such as the lack of oxygen, the cell activates a compensatory response called hypertrophy. This makes the heart grow and increase its contraction capacity. Once solved the problem, it stops signaling to activate hypertrophic genes. The problem arises when the stress does not disappear or there are mutations in some proteins that causes the signaling pathway to be constantly stimulated. That's when the pathology appears in the form of HCM.

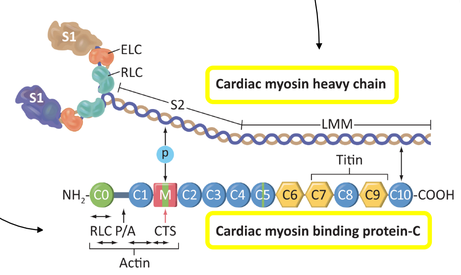


Harvey et al. (2011)

Sarcomeric protein mutations

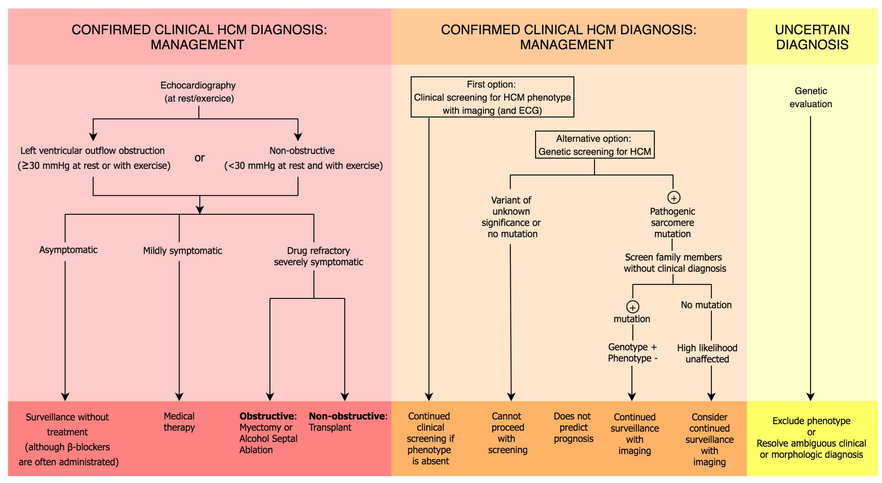


Maron et al. (2013)



Viswanathan et al. (2017)

Diagnosis

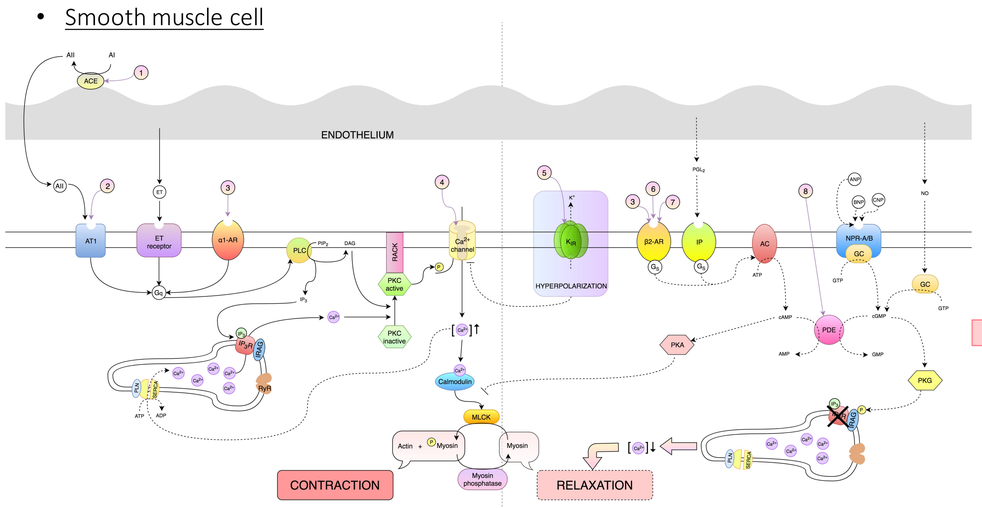


* There are certain biomarkers that indicate the onset of HCM such as natriuretic peptides and miRNAs. But they still need to be more studied in order to know how to use them correctly as diagnostic tools.

Modified from Maron et al. (2014)

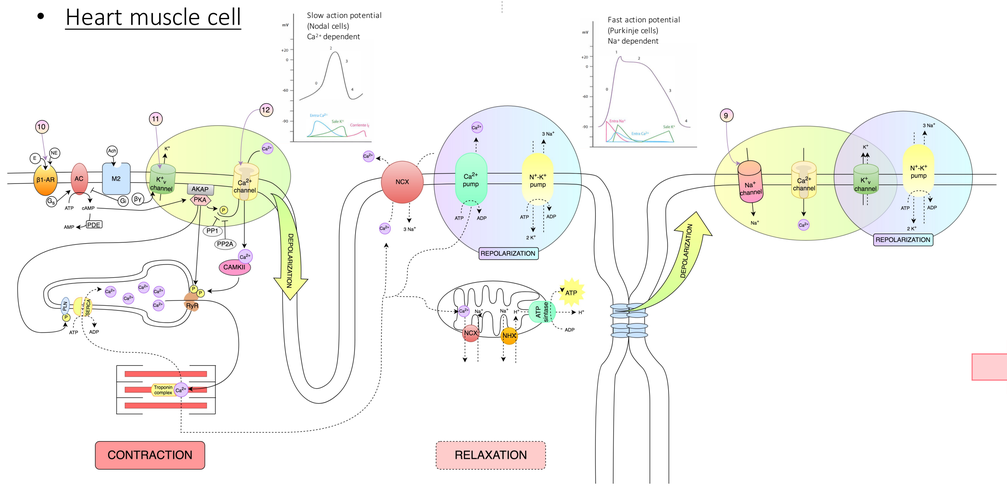
Pharmacological treatments

- Smooth muscle cell



Antihypertensives vasodilators	
Categories	Examples
1. ACE inhibitors	Captopril, Enalapril, Lisinopril, Ramipril.
2. AT1 antagonists	Losartan, Valsartan, Irbesartan.
3. Mixed β-blockers	Labetalol, Carvedilol.
4. Ca^{2+} channel antagonists	• Non dihydropiridinic Verapamil, Diltiazem. • Dihydropiridinic Amlodipine, Nifedipine, Felodipine, Nicardipine.
5. K_{IR} channel activators	Cromakalim, Pinacidil, Diazoxide.
6. Non-selective β-blockers	Alprenolol, Carteolol, Nadolol, Oxprenolol, Propranolol, Sotalol.
7. β2 selective β-blockers	Butoxamine, ICI 118551, α-methyl propanolol.
8. PDE inhibitors	Sildenafil, Vardenafil, Tadalafil.

- Heart muscle cell



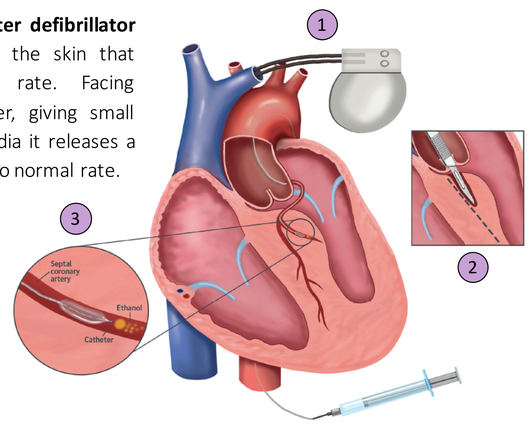
Antiarrhythmics		
Class	Categories	Examples
I	**9.** Na^+ channel blockers	• Ia Disopyramide, Procainamide, Quinidine. • Ib Lidocaine, Phenytoin. • Ic Flecainide, Propafenone.
II	**10.** β1 selective β-blockers	Atenolol, Acebutolol, Betaxolol, Esmolol, Metoprolol, Propanolol.
III	**11.** K^+ channel blockers	Amiodarone, Bretylium.
IV	**12.** Ca^{2+} channel blockers	Verapamil, Diltiazem.
V	Na^+-K^+ pump blockers	Digoxin.

Invasive treatments

1. An **automated implantable cardioverter defibrillator (AICD)** is a small device placed under the skin that measures and controls the heart rate. Facing bradyarrhythmia it acts as a pacemaker, giving small electric impulses, and in front a tachycardia it releases a much more powerful discharge to return to normal rate.

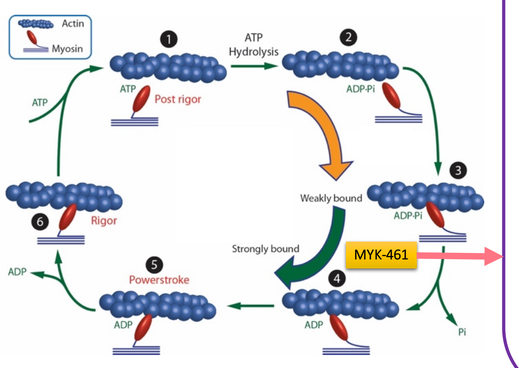
2. **Septal myectomy** is a surgical procedure that consists in making a longitudinal incision in the hypertrophic septum in order to decrease its thickness.

3. **Alcohol septal ablation** reduces the thickness of the septum using alcohol, which resects the tissue.



Modified from Liebregts et al. (2017)

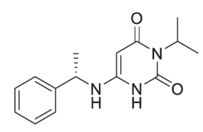
New inhibitory molecule for sarcomeric contraction



Cytoskeleton news. Nov/Dec 2012

It has been possible to synthesize a molecule called MYK-461 (commercial name: **Mavacampten**), which binds to the heavy chain of myosin and inhibits its ATPase function. By making the release of the inorganic phosphate slower, it is possible to reduce the contraction force.

It's still in phase II, but it's also giving good results. Apart from attenuating the contraction force, cell organization is recovered, hypertrophy of the ventricular walls is reversed and the number of genes affected by HCM is decreased.



Green et al. (2016)

Other treatments → **Gene therapy with viral vectors** and **induced pluripotent stem cells (iPSC)**. Both still require many years of research and need to be approved by regulatory agencies before they can be considered therapies to cure a disease.

Conclusions

Although hypertrophic cardiomyopathy affects many people, there are still no perfect diagnostic techniques or medicines to prevent or cure the disease. For the future, we should understand better how mutations and signaling pathways lead to the disease in order to find better treatments. These should be focused on regenerative therapies or molecules specifically targeted to sarcomeric proteins in order to inhibit hypercontraction.

References

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2. Green, E. M. et al. (2016). *A small-molecule inhibitor of sarcomere contractility suppresses hypertrophic cardiomyopathy in mice.* Science. 351(6273):617–621.
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4. Filgueiras-Rama, D., de Juan Bagudá, J., Jurado Román, A., & Loughlin Ramírez, G. (2014). *Cardiología y Cirugía Cardiovascular.* Madrid: CTO.