1. Int J Cardiol. 2018 Apr 15;257:344-350. doi: 10.1016/j.ijcard.2018.01.006.

Common presentation of rare diseases: Left ventricular hypertrophy and diastolic dysfunction.

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Left ventricular hypertrophy may be a consequence of a hemodynamic overload or a manifestation of several diseases affecting different structural and functional proteins of cardiomyocytes. Among these, sarcomeric hypertrophic cardiomyopathy (HCM) represents the most frequent cause. In addition, several metabolic diseases lead to myocardial thickening, either due to intracellular storage (glycogen storage and lysosomal diseases), extracellular deposition (TTR and AL amyloidosis) or due to abnormal energy metabolism (mitochondrial diseases). The recognition of these rare causes of myocardial hypertrophy is important for family screening strategies, risk assessment, and treatment. Moreover, as there are specific therapies for some forms of HCM including enzyme substitution and chaperone therapies and specific treatments for TTR amyloidosis, a differential diagnosis should be sought in all patients with unexplained left ventricular hypertrophy. Diastolic dysfunction is a key feature of HCM and its phenocopies. Its assessment is complex and requires evaluation of several functional parameters and structural changes. Severe diastolic dysfunction carries a negative prognostic implication and its value in differential diagnosis is limited.

2. Circulation. 2018 Mar 6;137(10):1015-1023. doi: 10.1161/CIRCULATIONAHA.117.030437. Epub 2017 Nov 30.

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BACKGROUND: Identification of people with hypertrophic cardiomyopathy (HCM) who are at risk of sudden cardiac death (SCD) and require a prophylactic implantable cardioverter defibrillator is challenging. In 2014, the European Society of Cardiology proposed a new risk stratification method based on a risk prediction model (HCM Risk-SCD) that estimates the 5-year risk of SCD. The aim was to externally validate the 2014 European Society of Cardiology recommendations in a geographically diverse cohort of patients recruited from the United States, Europe, the Middle East, and Asia.

METHODS: This was an observational, retrospective, longitudinal cohort study.

RESULTS: The cohort consisted of 3703 patients. Seventy three (2%) patients reached the SCD end point within 5 years of follow-up (5-year incidence, 2.4% [95% confidence interval {CI}, 1.9-3.0]). The validation study revealed a calibration slope of 1.02 (95% CI, 0.93-1.12), C-index of 0.70 (95% CI,

0.68-0.72), and D-statistic of 1.17 (95% CI, 1.05-1.29). In a complete case analysis (n= 2147; 44 SCD end points at 5 years), patients with a predicted 5-year risk of <4% (n=1524; 71%) had an observed 5-year SCD incidence of 1.4% (95% CI, 0.8-2.2); patients with a predicted risk of ≥6% (n=297; 14%) had an observed SCD incidence of 8.9% (95% CI, 5.96-13.1) at 5 years. For every 13 (297/23) implantable cardioverter defibrillator implantations in patients with an estimated 5-year SCD risk ≥6%, 1 patient can potentially be saved from SCD.

CONCLUSIONS: This study confirms that the HCM Risk-SCD model provides accurate prognostic information that can be used to target implantable cardioverter defibrillator therapy in patients at the highest risk of SCD.

3. Int J Cardiol. 2017 Nov 1;246:55. doi: 10.1016/j.ijcard.2017.03.107.

Reply to: Is subcutaneous implantable cardioverter-defibrillator testing effective and safe for patients with hypertrophic cardiomyopathy?

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Comment on Int J Cardiol. 2017 Nov 1;246:54, Int J Cardiol. 2017 Mar 15;231:115-119.

4. JAMA Cardiol. 2017 Oct 1;2(10):1147-1151. doi: 10.1001/jamacardio.2017.2353.

Intraoperative Diagnosis of Anderson-Fabry Disease in Patients With Obstructive Hypertrophic Cardiomyopathy Undergoing Surgical Myectomy.

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Importance: Diagnostic screening for Anderson-Fabry cardiomyopathy (AFC) is performed in the presence of specific clinical red flags in patients with hypertrophic cardiomyopathy (HCM) older than 25 years. However, left ventricular outflow tract obstruction (LVOTO) has been traditionally considered an exclusion criteria for AFC.

Objective: To examine a series of patients diagnosed with HCM and severe basal LVOTO undergoing myectomy in whom the diagnosis of AFC was suspected by the cardiac surgeon intraoperatively and confirmed by histological and genetic examinations. Design, Setting, and Participants: This retrospective analysis of patients undergoing surgical septal reduction strategies was conducted in 3 European tertiary referral centers for HCM from July 2013 to December 2016. Patients with a clinical diagnosis of obstructive HCM referred for surgical management of LVOTO were observed for at least 18 months after the procedure (mean [SD] follow-up, 33 [14] months).

Main Outcomes and Measures: Etiology of patients with HCM who underwent surgical myectomy.

Results: From 2013, 235 consecutive patients with a clinical diagnosis of HCM underwent septal myectomy. The cardiac surgeon suspected a storage disease in 3 patients (1.3%) while inspecting their heart samples extracted from myectomy. The mean (SD) age at diagnosis for these 3 patients was 42 (4) years; all were male. None of the 3 patients presented with extracardiac features suggestive of AFC. All patients showed asymmetrical left ventricular hypertrophy, with maximal left ventricular thickness in the basal septum (19-31 mm), severe basal LVOTO (70-120 mm Hg), and left atrial dilatation (44-57 mm). Only 1 patient presented with late gadolinium enhancement on cardiovascular magnetic resonance at the right ventricle insertion site. The mean (SD) age at surgical procedure was 63 (5) years. On tactile sensation, the surgeon felt a spongy consistency of thesurgical samples, different from the usual stony-elastic consistency typical of classic HCM, and this prompted histological examinations. Histology showed evidence of intracellular storage, and genetic analysis confirmed a GLA A gene mutation (p.Asn215Ser) in all 3 patients.

Conclusions and Relevance: Screening for AFC should be performed even in the absence of red flags in patients with HCM older than 25 years.

5. Int J Cardiol. 2017 Jun 1;236:249-252. doi: 10.1016/j.ijcard.2017.02.027. Epub 2017 Feb 10.

Cardiovascular screening in low-income settings using a novel 4-lead smartphone-based electrocardiograph (D-Heart®).

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BACKGROUND: MHealth technologies are revolutionizing cardiovascular medicine. However, a low-cost, user-friendly smartphone-based electrocardiograph is still lacking. D-Heart® is a portable device that enables the acquisition of the ECG on multiple leads which streams via Bluetooth to any smartphone. Because of the potential impact of this technology in low-income settings, we determined the accuracy of D-Heart® tracings in the stratification of ECG morphological abnormalities, compared with 12-lead ECGs.

METHODS: Consecutive African patients referred to the Ziguinchor Regional Hospital (Senegal) were enrolled (n=117; 69 males, age 39±11years). D-Heart® recordings (3 peripheral leads plus V5) were obtained immediately followed by 12 lead ECGs and were assessed blindly by 2 independent observers. Global burden of ECG abnormalities was defined by a semi-quantitative score based on the sum of 9 criteria, identifying four classes of increasing severity.

RESULTS: D-Heart® and 12-lead ECG tracings were respectively classified as: normal: 72 (61%) vs 69 (59%); mildly abnormal: 42 (36%) vs 45 (38%); moderately abnormal: 3 (3%) vs 3 (3%). None had markedly abnormal tracings. Cohen's weighted kappa (kw) test demonstrated a concordance of 0,952 ($p<0,001$, agreement 98,72%). Concordance was high as well for the Romhilt-Estes score ($kw=0,893$; $p<0,001$ agreement 97,35%). PR and QRS intervals comparison with Bland-Altman method showed good accuracy for D-Heart® measurements (95% limit of agreement ±20ms for PR and ±10ms for QRS).

CONCLUSIONS: D-Heart® proved effective and accurate stratification of ECG abnormalities omparable to the 12-lead electrocardiographs, thereby opening new perspectives for low-cost community cardiovascular screening programs in low-income settings.

6. Int J Cardiol. 2017 Mar 15;231:115-119. doi: 10.1016/j.ijcard.2016.12.187. Epub 2017 Jan 4.

Effectiveness of subcutaneous implantable cardioverter-defibrillator testing in patients with hypertrophic cardiomyopathy.

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Comment in Int J Cardiol. 2017 Nov 1;246:54, Int J Cardiol. 2017 Nov 1;246:55.

BACKGROUND: Subcutaneous ICD (S-ICD) is a promising option for Hypertrophic Cardiomyopathy (HCM) patients at risk of Sudden Cardiac Death (SCD). However, its effectiveness in terminating ventricular arrhythmias in HCM is yet unresolved.

METHODS: Consecutive HCM patients referred for S-ICD implantation were prospectively enrolled. Patients underwent one or two attempts of VF induction by the programmer. Successful conversion was defined as any 65J shock that terminated VF (not requiring rescue shocks). Clinical and instrumental parameters were analyzed to study predictors of conversion failure.

RESULTS: Fifty HCM patients (34 males, 40±16years) with a mean BMI of 25.2±4.4kg/m2 were evaluated. Mean ESC SCD risk of was 6.5±3.9% and maximal LV wall thickness (LVMWT) was 26±6mm. In 2/50 patients no arrhythmias were inducible, while in 7 (14%) only sustained ventricular tachycardia was induced and cardioverted. In the remaining 41 (82%) patients, 73 VF episodes were induced (1 episode in 14 and >1 in 27 patients). Of these, 4 (6%) spontaneously converted. In 68/69 (98%) the S-ICD successfully cardioverted, but failed in 1 (2%) patient, who needed rescue defibrillation. This patient was severely obese (BMI 36) and LVMWT of 25mm. VF was re-induced and successfully converted by the 80J reversed polarity S-ICD.

CONCLUSIONS: Acute DT at 65J at the implant showed the effectiveness of S-ICD in the recognition and termination of VT/VF in all HCM patients except one. Extreme LVH did not affect the performance of the device, whereas severe obesity was likely responsible for the single 65J failure.

7. Eur J Nucl Med Mol Imaging. 2017 May;44(5):866-875. doi: 10.1007/s00259-016-3603-2. Epub 2017 Jan 3.

Myocardial blood flow and left ventricular functional reserve in hypertrophic cardiomyopathy: a 13NH3 gated PET study.

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Comment in Eur J Nucl Med Mol Imaging. 2017 May;44(5):861-865.

INTRODUCTION: Ischemia in hypertrophic cardiomyopathy (HCM) is caused by coronary microvascular dysfunction (CMD), which is detected by measuring myocardial blood flow (MBF) with PET. Whether CMD may be associated with ischemic left ventricular (LV) dysfunction is unclear. We therefore assessed LV ejection fraction (EF) reserve in HCM patients undergoing dipyridamole (Dip) PET.

METHODS: Resting and stress 13NH3 dynamic as well as gated PET were performed in 34 HCM patients. Segmental MBF and transmural perfusion gradient (TPG = subendocardial / subepicardial MBF) were assessed. LVEF reserve was considered abnormal if Dip LVEF decreased more than 5 units as compared to rest.

RESULTS: Eighteen patients had preserved (group A) and 16 abnormal LVEF reserve (group B; range -7 to -32). Group B patients had greater wall thickness than group A, but resting volumes, LVEF, resting and Dip MBF, and myocardial flow eserve were similar. Group B had slightly higher summed stress score and summed difference score in visual analysis than group A, and a significantly highersummed stress wall motion score. In group B, resting TPG was slightly lower (1.31 ± 0.29 vs. 1.37 ± 0.34, $p < 0.05$), and further decreased after Dip, whilst in group A it increased (B = 1.20 ± 0.39, $p < 0.0001$ vs. rest and vs. A = 1.40 ± 0.43). The number of segments per patient with TPG <1 was higher than in group A ($p < 0.001$) and was a significant predictor of impaired LVEF reserve (OR 1.86, $p < 0.02$), together with wall thickness (OR 1.3, $p < 0.02$).

CONCLUSION: Abnormal LVEF response is common in HCM patients following Dip, and is related to abnormal TPG, suggesting that subendocardial ischemia might occur under Dip and cause transient LV dysfunction. Although in vivo this effect may be hindered by the adrenergic drive associated with effort, these findings may have relevance in understanding exercise limitation and heart failure symptoms in HCM.

8. Eur J Nucl Med Mol Imaging. 2016 Dec;43(13):2413-2422. Epub 2016 Aug 16.

Role of quantitative myocardial positron emission tomography for risk stratification in patients with hypertrophic cardiomyopathy: a 2016 reappraisal.

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AIMS: Myocardial blood flow <1.1 mL/min/g following dipyridamole (Dip-MBF)

assessed by positron emission tomography (PET) was identified in 2003 as an important outcome predictor in hypertrophic cardiomyopathy (HCM), based on scans performed in the 90s. However, such extreme Dip-MBF impairment is rarely observed in contemporary cohorts. We, therefore, reassessed the Dip-MBF threshold defining high-risk HCM patients.

METHODS: Dip-MBF was measured using 13N-ammonia in 100 HCM consecutive patients, prospectively enrolled and followed for 4.0 ± 2.2 years. Outcome was assessed based on tertiles of Dip-MBF. The study end-point was a combination of cardiovascular death, progression to severe functional limitation, cardioembolic stroke, life-threatening ventricular arrhythmias.

RESULTS: Global Dip-MBF was 1.95 ± 0.85, ranging from 0.7 to 5.9 mL/min/g. Dip-MBF tertile cut-off values were: 0.73 to 1.53 mL/min/g (lowest), 1.54 to 2.13 mL/min/g (middle), and 2.14 to 5.89 mL/min/g (highest). During follow-up, lowest tertile Dip-MBF was associated with sevenfold independent risk of unfavorable outcome compared to the other two tertiles. Dip-MBF 1.35 mL/min/g was identified as the best threshold for outcome prediction. Regional perfusion analysis showed that all cardiac deaths (n = 4) occurred in patients in the lowest tertile of lateral wall Dip-MBF (≤1.72 mL/min/g); septal Dip-MBF was not predictive.

CONCLUSIONS: Dip-MBF confirms its role as potent predictor of outcome in HCM. However, the threshold for prediction in a contemporary cohort is higher than that reported in earlier studies. Dip-MBF impairment in the lateral wall, possibly reflecting diffuse disease extending to non-hypertrophic regions, is a sensitive predictor of mortality in HCM.

9. Circ Heart Fail. 2016 Sep;9(9). pii: e003090. doi: 10.1161/CIRCHEARTFAILURE.116.003090.

Histological and Histometric Characterization of Myocardial Fibrosis in End-Stage Hypertrophic Cardiomyopathy: A Clinical-Pathological Study of 30 Explanted Hearts.

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BACKGROUND: Although noninvasively detected myocardial fibrosis (MF) has clinical implications in hypertrophic cardiomyopathy, the extent, type, and distribution of ventricular MF have never been extensively pathologically characterized. We assessed the overall amount, apex-to-base, circumferential, epicardial-endocardial distribution, pattern, and type of MF in 30 transplanted hearts of end-stage, hypertrophic cardiomyopathy.

METHODS AND RESULTS: Visual and morphometric histological analyses at basal, midventricular, and apical levels were performed. Overall MF ranged from 23.1% to 55.9% (mean=37.3±8.4%).

Prevalent types of MF were as follows: replacement in 53.3%, interstitial-perimyocyte in 13.3%, and mixed in 33.3%. Considering left ventricular base-to-apex distribution, MF was 31.9%, 43%, and 46.2% at basal, midventricular, and apical level, respectively (P<0.001). Circumferential distributions (mean percentage of MF within the section) were as follows: anterior 11.9%, anterolateral 15.8%, inferolateral 7.0%, inferior 24.3%, anteroseptal 11%, midseptal 10.7%, and posteroseptal 11.4%; circumferential distributions for anterior and inferior right ventricular walls were 3.4% and 4.5%, respectively. Epicardial-endocardial distributions were as follows: trabecular 26.1% and subendocardial 20.2%, midwall 33.4%, and subepicardial 20.3%. Main patterns identified were as follows: midwall in 33.3% of the hearts, transmural in 23.3%, midwall-subepicardial in 23.3%, and midwall-subendocardial in 20%.

CONCLUSIONS: In end-stage, hypertrophic cardiomyopathy patients undergoing transplantation, more than one-third of the left ventricular myocardium was replaced by fibrosis, mainly of replacement type. MF preferentially involved the left ventricular apex and the midwall. Inferior and anterior walls and septum were maximally involved, whereas inferolateral and right ventricular were usually spared. These observations reflect the complex pathophysiology of hypertrophic cardiomyopathy and may provide clues for the timely recognition of disease progression by imaging techniques capable of quantifying MF.

10. Am J Cardiol. 2016 Aug 1;118(3):432-9. doi: 10.1016/j.amjcard.2016.05.023. Epub 2016 May 15.

Usefulness of Electrocardiographic Patterns at Presentation to Predict Long-term Risk of Cardiac Death in Patients With Hypertrophic Cardiomyopathy.

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The objective of this study was to investigate the prognostic significance of 12-lead electrocardiogram (ECG) patterns in a large multicenter cohort of patients with hypertrophic cardiomyopathy; 1,004 consecutive patients with hypertrophic cardiomyopathy and a recorded standard ECG (64% men, mean age 50 ± 16 years) were evaluated at 4 Italian centers. The study end points were sudden cardiac death (SCD) or surrogates, including appropriate implanted cardiac defibrillator discharge and resuscitated cardiac arrest and major cardiovascular events (including SCD or surrogates and death due to heart failure, cardioembolic stroke, or heart transplantation). Prevalence of baseline electrocardiographic characteristics was: normal ECG 4%, ST-segment

depression 56%, pseudonecrosis waves 33%, "pseudo-ST-segment elevation myocardial infarction (STEMI)" pattern 17%, QRS duration ≥120 ms 17%, giant inverted T waves 6%, and low QRS voltages 3%. During a mean follow-up of 7.4 ± 6.8 years, 77 patients experienced SCD or surrogates and 154 patients experienced major cardiovascular events. Independent predictors of SCD or surrogates were unexplained syncope (hazard ratio [HR] 2.5, 95% confidence interval [CI] 1.4 to 4.5, p = 0.003), left ventricular ejection fraction <50% (HR 3.5, 95% CI 1.9 to 6.7, p = 0.0001), nonsustained ventricular tachycardia (HR 1.7, 95% CI 1.1 to 2.6, p = 0.027), pseudo-STEMI pattern (HR 2.3, 95% CI 1.4 to 3.8, p = 0.001), QRS duration ≥120 ms (HR 1.8, 95% CI 1.1 to 3.0, p = 0.033), and low QRS voltages (HR 2.3, 95% CI 1.01 to 5.1, p = 0.048). Independent predictors of major cardiovascular events were age (HR 1.02, 95% CI 1.01 to 1.03, p = 0.0001), LV ejection fraction <50% (HR 3.73, 95% CI 2.39 to 5.83, p = 0.0001), pseudo-STEMI pattern (HR 1.66, 95% CI 1.13 to 2.45, p = 0.010), QRS duration ≥120 ms (HR 1.69, 95% CI 1.16 to 2.47, p = 0.007), and prolonged QTc interval (HR 1.68, 95% CI 1.21 to 2.34, p = 0.002). In conclusion, a detailed qualitative and quantitative electrocardiographic analyses provide independent predictors of prognosis that could be integrated with the available score systems to improve the power of the current model.

11. Eur J Heart Fail. 2016 Sep;18(9):1106-18. doi: 10.1002/ejhf.541. Epub 2016 Apr 24.

Pharmacological treatment of hypertrophic cardiomyopathy: current practice and novel perspectives.

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Hypertrophic cardiomyopathy (HCM) is entering a phase of intense translational research that holds promise for major advances in disease-specific pharmacological therapy. For over 50 years, however, HCM has largely remained an orphan disease, and patients are still treated with old drugs developed for other conditions. While judicious use of the available armamentarium may control the clinical manifestations of HCM in most patients, specific experience is required in challenging situations, including deciding when not to treat. The present review revisits the time-honoured therapies available for HCM, in a practical perspective reflecting real-world scenarios. Specific agents are presented with doses, titration strategies, pros and cons. Peculiar HCM dilemmas such as treatment of dynamic outflow obstruction, heart failure caused by end-stage progression and prevention of atrial fibrillation and ventricular arrhythmias are assessed. In the near future, the field of HCM drug therapy will rapidly expand, based on ongoing efforts. Approaches such as myocardial metabolic modulation, late sodium current inhibition and allosteric myosin inhibition have moved from pre-clinical to clinical research, and reflect a surge of scientific as well as economic interest by academia and industry alike. These exciting developments, and their implications for future research, are discussed.

12. Am J Cardiol. 2016 Apr 1;117(7):1151-9. doi: 10.1016/j.amjcard.2015.12.058. Epub 2016 Jan 14.

Impact of Genotype on the Occurrence of Atrial Fibrillation in Patients With Hypertrophic Cardiomyopathy.

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Genes associated with hypertrophic cardiomyopathy (HC) are not uniformly expressed in the atrial myocardium. Whether this may impact susceptibility to atrial fibrillation (AF) is unresolved. To analyze the prevalence and clinical correlates of AF in relation to genotype in a large HC cohort, prevalence and clinical profile of AF were assessed in 237 patients with HC, followed for 14 ±10 years. Patients were divided into 3 genetic subgroups: (1) MYBPC3 (58%), (2) MYH7 (28%), and (3) "other genotypes" (14%; comprising TNNT2, TNNI3, TPM1, MYL2, complex genotypes, Z-line, and E-C coupling genes). Left atrial size was similar in the 3 subsets. AF occurred in 74 patients with HC (31%), with no difference among groups (31% in MYBPC3, 37% in MYH7 and 18% in other genotypes, p = 0.15), paroxysmal/persistent AF (12%, 18%, and 12%, respectively; p = 0.53), paroxysmal/persistent evolved to permanent (12%, 12%, and 3%, p = 0.36) or permanent AF (7%, 7%, and 3%, p = 0.82). Age at AF onset was younger in the group with other genotypes (37 ± 10 years) compared to the first 2 groups (53 ± 14 and 51 ± 17, respectively; p = 0.05) because of early onset associated with complex genotypes and a specific JPH2 mutation associated with abnormal intracellular calcium handling. At multivariate analysis, independent predictors of AF were atrial diameter (p ≤0.05) and age at diagnosis (p = 0.09), but not genetic subtype (p = 0.35). In conclusion, in patients with HC, genetic testing cannot be used in clinical decision making with regard to management strategies for AF. Genotype is not predictive of onset or severity of AF, which appears rather driven by hemodynamic determinants of atrial dilatation. Exceptions are represented by rare genes suggesting specific molecular pathways for AF in genetic cardiomyopathies.

13. G Ital Cardiol (Rome). 2015 Nov;16(11):630-8. doi: 10.1714/2066.22434.

[Heart involvement in Anderson-Fabry disease: Italian recommendations for diagnostic, follow-up and therapeutic management]. [Article in Italian]

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Anderson-Fabry disease is a rare X-linked lysosomal storage disorder caused by mutations of the GLA gene that encodes alpha-galactosidase A. It is characterized by a multisystemic involvement: the renal, neurological, heart, cochleovestibular and cutaneous systems are the most damaged. Morbidity and mortality of Anderson-Fabry disease depend on renal insufficiency, heart failure and nervous system involvement. Left ventricular hypertrophy is the most common cardiac manifestation followed by conduction system disease, valve dysfunction, and arrhythmias. Mild to moderate left ventricular hypertrophy may simulate a non-obstructive hypertrophic cardiomyopathy. Management of Anderson-Fabry disease starting from the diagnosis of cardiac involvement, the prevention of complications, the therapeutic aspects, up to appropriate clinical follow-up, requires a multidisciplinary approach. According to recent management guidelines, only few evidence-based data are available to guide the clinical and therapeutic approach to this rare disease. An Italian Board, composed by nephrologists, cardiologists, geneticists, pediatricians and neurologists has been established in order to approve by consensus a diagnostic and therapeutic management protocol. The authors report the results of this cardiologic management consensus.

14. Circ Heart Fail. 2015 Nov;8(6):1014-21. doi: 10.1161/CIRCHEARTFAILURE.114.001843. Epub 2015 Oct 7.

Clinical Spectrum, Therapeutic Options, and Outcome of Advanced Heart Failure in Hypertrophic Cardiomyopathy.

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BACKGROUND: The clinical course of patients with hypertrophic cardiomyopathy and advanced heart failure (HF) subtended by progressive left ventricular dysfunction has received limited attention. Our aim was to assess the outcome of HF and impact of treatment options including the implantable cardioverter-defibrillator and heart transplantation (HT) in patients with hypertrophic cardiomyopathy evaluated at 2 Italian referral centers >3 decades.

METHODS AND RESULTS: All-cause mortality and a combined end point including death, HT, or appropriate implantable cardioverter-defibrillator shock were assessed in 71 consecutive patients with HF not related to outflow obstruction (7% of the entire hypertrophic cardiomyopathy cohort) followed up for 6.1±6.9 years after development of New York Heart Association class III to IV symptoms. At enrollment, left ventricular ejection fraction was <50% in 55 patients and >50% in 16; all had restrictive left ventricular filling. During follow-up, 35 patients died (49%%; 5-year rate, 49%) and 53 met the combined end point (75%; 5-year rate, 62%). Most events occurred in the 3 years after HF onset (17% per year compared with only 3% per year subsequently). Appropriate implantable cardioverter-defibrillator shocks occurred in 11 of 34 implanted patients. Of 37 patients evaluated for HT, 14 were transplanted, 10 listed, and 13 excluded; 2 early post-HT deaths occurred in patients with elevated pulmonary vascular resistance. Eleven of the 14 HT patients were alive at 10±8 years.

CONCLUSIONS: In hypertrophic cardiomyopathy, advanced HF not associated with outflow obstruction portends a severely unfavorable prognosis, particularly in the first 3 years after onset of symptoms, despite frequently preserved systolic function in about one quarter of the patients. Outcome of HT is favorable but requires early consideration, as the window of opportunity may be short.

15. Heart Rhythm. 2016 Feb;13(2):457-63. doi: 10.1016/j.hrthm.2015.09.007. Epub 2015 Sep 8.

Prevalence of subcutaneous implantable cardioverter-defibrillator candidacy based on template ECG screening in patients with hypertrophic cardiomyopathy.

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BACKGROUND: Subcutaneous implantable cardioverter-defibrillator (S-ICD) is a promising option for patients with hypertrophic cardiomyopathy (HCM). Patients with HCM can present markedly abnormal electrocardiograms (ECGs), and there are no data on what percentage of patients with HCM fail the prerequisite S-ICD vector screening.

OBJECTIVE: The purpose of this study was to determine the failure rate of the prerequisite vector screening using 1 or 2 acceptable vectors stratified for risk profile for sudden cardiac death and predictors of failure.

METHODS: ECG recordings from consecutive patients with HCM simulating the S-ICD sensing vectors were analyzed with the S-ICD screening tool. Eligibility was defined by 1 or 2 appropriate vectors. Medical history, ultrasound characteristics, and 12-lead ECG characteristics were analyzed and the individual arrhythmic risk at 5 year was determined to study potential predictors of failure.

RESULTS: One hundred sixty-five (118 men; mean age 51 ± 16 years) patients were analyzed. Twenty-two patients (13%) had a high risk of sudden cardiac death, 33 (20%) had intermediate to high risk, and 110 (67%) had low risk. Twenty-six patients (16%) had no suitable vector, including 8 of 22 high-risk patients (36%). The primary cause of failure was high T-wave voltages in 25% of the vectors analyzed. T-wave inversions in >2 leads on the surface 12-lead ECG (odds ratio 15.6; 95% confidence interval 4.9-50.3; P < .001) and prior myectomy (odds ratio 8.4; 95% confidence interval 2.1-33.1; P = .002) were significantly associated with screening failure in a multivariable model.

CONCLUSION: Currently available preimplant screening algorithms recommended by the manufacturer are associated with a significant failure rate in patients with HCM, particularly in the high-risk subgroup.

16. Eur J Nucl Med Mol Imaging. 2015 Sep;42(10):1581-8. doi: 10.1007/s00259-015-3101-y. Epub 2015 Jun 27.

Validation of pixel-wise parametric mapping of myocardial blood flow with $^{13}NH_3$ PET in patients with hypertrophic cardiomyopathy.

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Comment in Eur J Nucl Med Mol Imaging. 2015 Nov;42(12):1899-902.

PURPOSE: Transmural abnormalities in myocardial blood flow (MBF) are important causes of ischaemia in patients with left ventricular (LV) hypertrophy. The study aimed to test whether pixel-wise parametric mapping of (13)NH3 MBF can reveal transmural abnormalities in patients with hypertrophic cardiomyopathy (HCM).

METHODS: We submitted 11 HCM patients and 9 age-matched controls with physiological LV hypertrophy to rest and stress (dipyridamole) (13)NH3 PET. We measured MBF using a compartmental model, and obtained rest and stress parametric maps. Pixel MBF values were reorganized to obtain subendocardial and subepicardial MBF of LV segments.

RESULTS: MBF at rest was higher in the subendocardial than in the subepicardial layer: 0.78 ± 0.19 vs. 0.60 ± 0.18 mL/min/g in HCM patients; 0.92 ± 0.24 vs. 0.75 ± 0.24 mL/min/g in controls (both p < 0.0001). Transmural perfusion gradient (TPG = subendocardial MBF/subepicardial MBF) at rest was similar: 1.35 ± 0.31 in HCM patients; 1.28 ± 0.27 in controls (NS). During stress, controls maintained higher subendocardial MBF: 2.44 ± 0.54 vs. 1.96 ± 0.67 mL/min/g tissue (p < 0.0001), with a TPG of 1.33 ± 0.35 (NS vs. rest). In HCM patients, the difference between subendocardial and subepicardial MBF was reduced (1.46 ± 0.48

vs. 1.36 ± 0.48 mL/min/g tissue, p < 0.01) and TPG decreased to 1.11 ± 0.34 (p < 0.0001 vs. rest and vs. controls). In HCM patients 8 of 176 segments had subendocardial MBF less than -2 × SD of the mean, versus none of 144 segments in controls (p < 0.01).

CONCLUSION: Pixel-wise parametric mapping of (13)NH3 MBF enables the identification of transmural abnormalities in patients with HCM.

17. J Cardiovasc Transl Res. 2015 Jun;8(4):232-43. doi: 10.1007/s12265-015-9624-6. Epub 2015 May 14.

An Investigation of the Molecular Mechanism of Double cMyBP-C Mutation in a Patient with End-Stage Hypertrophic Cardiomyopathy.

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Mutations in the gene coding for cardiac myosin binding protein-C (cMyBP-C), a multi-domain (C0-C10) protein, are a major causative factor for inherited hypertrophic cardiomyopathy. Patients carrying mutations in this gene have an extremely heterogeneous clinical course, with some progressing to end-stage heart failure. The cause of this variability is unknown. We here describe molecular modeling of a double mutation in domains C1 (E258K) and C2 (E441K) in a patient with severe HCM phenotype. The three-dimensional structure for the C1-motif-C2 complex was constructed with double and single mutations being introduced. Molecular dynamic simulations were performed for 10 ns under physiological conditions. The results showed that both E258K and E441K in isolation can predominantly affect the native domain as well as the nearby motif via conformational changes and result in an additive effect when they coexist. These changes involve important regions of the motif such as phosphorylation and potential actin-binding sites. Moreover, the charge reversal mutations altered the surface electrostatic properties of the complex. In addition, we studied protein expression, which showed that the mutant proteins were expressed and we can suppose that the severe phenotype was not due to haploinsufficiency. However, additional studies on human gene expression will need to confirm this hypothesis. The double mutation affecting the regulatory N-terminal of cMyBP-C have the potential of synergistically interfering with the binding to neighbouring domains and other sarcomeric proteins. These effects may account for the severe phenotype and clinical course observed in the complex cMyBP-C genotypes.

18. Orphanet J Rare Dis. 2015 Mar 27;10:36. doi: 10.1186/s13023-015-0253-6.

Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document.

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INTRODUCTION: Fabry disease (FD) is a lysosomal storage disorder resulting in progressive nervous system, kidney and heart disease. Enzyme replacement therapy (ERT) may halt or attenuate disease progression. Since administration is burdensome and expensive, appropriate use is mandatory. We aimed to define European consensus recommendations for the initiation and cessation of ERT in patients with FD.

METHODS: A Delphi procedure was conducted with an online survey (n = 28) and a meeting (n = 15). Patient organization representatives were present at the meeting to give their views. Recommendations were accepted with ≥75% agreement and no disagreement.

RESULTS: For classically affected males, consensus was achieved that ERT is recommended as soon as there are early clinical signs of kidney, heart or brain involvement, but may be considered in patients of ≥16 years in the absence of clinical signs or symptoms of organ involvement. Classically affected females and males with non-classical FD should be treated as soon as there are early clinical signs of kidney, heart or brain involvement, while treatment may be considered in females with non-classical FD with early clinical signs that are considered to be due to FD. Consensus was achieved that treatment should not be withheld from patients with severe renal insufficiency (GFR < 45 ml/min/1.73 m(2)) and from those on dialysis or with cognitive decline, but carefully considered on an individual basis. Stopping ERT may be considered in patients with end stage FD or other co-morbidities, leading to a life expectancy of <1 year. In those with cognitive decline of any cause, or lack of response for 1 year when the sole indication for ERT is neuropathic pain, stopping ERT may be considered. Also, in patients with end stage renal disease, without an option for renal transplantation, in combination with advanced heart failure (NYHA class IV), cessation of ERT should be considered. ERT in patients who are non-compliant or fail to attend regularly at visits should be stopped.

CONCLUSION: The recommendations can be used as a benchmark for initiation and cessation of ERT, although final decisions should be made on an individual basis. Future collaborative efforts are needed for optimization of these recommendations.

19. J Am Coll Cardiol. 2014 Dec 23;64(24):2589-2600. doi: 10.1016/j.jacc.2014.09.059.

Clinical phenotype and outcome of hypertrophic cardiomyopathy associated with thin-filament gene mutations.

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Comment in J Am Coll Cardiol. 2014 Dec 23;64(24):2601-4.

BACKGROUND: Mild hypertrophy but increased arrhythmic risk characterizes the stereotypic phenotype proposed for hypertrophic cardiomyopathy (HCM) caused by thin-filament mutations. However, whether such clinical profile is different from more prevalent thick-filament-associated disease is unresolved.

OBJECTIVES: This study aimed to assess clinical features and outcomes in a large cohort of patients with HCM associated with thin-filament mutations compared with thick-filament HCM.

METHODS: Adult HCM patients (age >18 years), 80 with thin-filament and 150 with thick-filament mutations, were followed for an average of 4.5 years.

RESULTS: Compared with thick-filament HCM, patients with thin-filament mutations showed: 1) milder and atypically distributed left ventricular (LV) hypertrophy (maximal wall thickness 18 ± 5 mm vs. 24 ± 6 mm; $p < 0.001$) and less prevalent outflow tract obstruction (19% vs. 34%; $p = 0.015$); 2) higher rate of progression to New York Heart Association functional class III or IV (15% vs. 5%; $p = 0.013$); 3) higher prevalence of systolic dysfunction or restrictive LV filling at last evaluation (20% vs. 9%; $p = 0.038$); 4) 2.4-fold increase in prevalence of triphasic LV filling pattern (26% vs. 11%; $p = 0.002$); and 5) similar rates of malignant ventricular arrhythmias and sudden cardiac death ($p = 0.593$).

CONCLUSIONS: In adult HCM patients, thin-filament mutations are associated with increased likelihood of advanced LV dysfunction and heart failure compared with thick-filament disease, whereas arrhythmic risk in both subsets is comparable. Triphasic LV filling is particularly common in thin-filament HCM, reflecting profound diastolic dysfunction.

20. Int J Cardiol. 2014 Dec 15;177(2):400-8. doi: 10.1016/j.ijcard.2014.09.001. Epub 2014 Sep 20.

Uncertain diagnosis of Fabry disease: consensus recommendation on diagnosis in adults with left ventricular hypertrophy and genetic variants of unknown significance.

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BACKGROUND: Screening in subjects with left ventricular hypertrophy (LVH) reveals a high prevalence of Fabry disease (FD). Often, a diagnosis is uncertain because characteristic clinical features are absent and genetic variants of unknown significance (GVUS) in the α-galactosidase A (GLA) gene are identified. This carries a risk of misdiagnosis, inappropriate counselling and extremely expensive treatment. We developed a diagnostic algorithm for adults with LVH (maximal wall thickness (MWT) of >12 mm), GLA GVUS and an uncertain diagnosis of FD.

METHODS: A Delphi method was used to reach a consensus between FD experts. We performed a systematic review selecting criteria on electrocardiogram, MRI and echocardiography to confirm or exclude FD. Criteria for a definite or uncertain diagnosis and a gold standard were defined.

RESULTS: A definite diagnosis of FD was defined as follows: a GLA mutation with ≤ 5% GLA activity (leucocytes, mean of reference value, males only) with ≥ 1 characteristic FD symptom or sign (neuropathic pain, cornea verticillata, angiokeratoma) or increased plasma (lyso)Gb3 (classical male

range) or family members with definite FD. Subjects with LVH failing these criteria have a GVUS and an uncertain diagnosis. The gold standard was defined as characteristic storage in an endomyocardial biopsy on electron microscopy. Abnormally low voltages on ECG and severe LVH (MWT>15 mm) <20 years exclude FD. Other criteria were rejected due to insufficient evidence.

CONCLUSIONS: In adults with unexplained LVH and a GLA GVUS, severe LVH at young age and low voltages on ECG exclude FD. If absent, an endomyocardial biopsy with electron microscopy should be performed.

21. Circ Cardiovasc Genet. 2014 Dec;7(6):741-50. doi: 10.1161/CIRCGENETICS.113.000486. Epub 2014 Aug 30.

Novel α-actinin 2 variant associated with familial hypertrophic cardiomyopathy and juvenile atrial arrhythmias: a massively parallel sequencing study.

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BACKGROUND: Next-generation sequencing might be particularly advantageous in genetically heterogeneous conditions, such as hypertrophic cardiomyopathy (HCM), in which a considerable proportion of patients remain undiagnosed after Sanger. In this study, we present an Italian family with atypical HCM in which a novel disease-causing variant in α-actinin 2 (ACTN2) was identified by next-generation sequencing.

METHODS AND RESULTS: A large family spanning 4 generations was examined, exhibiting an autosomal dominant cardiomyopathic trait comprising a variable spectrum of (1) midapical HCM with restrictive evolution with marked biatrial dilatation, (2) early-onset atrial fibrillation and atrioventricular block, and (3) left ventricular noncompaction. In the proband, 48 disease genes for HCM, selected on the basis of published reports, were analyzed by targeted resequencing with a customized enrichment system. After bioinformatics analysis, 4 likely pathogenic variants were identified: TTN c.21977G>A (p.Arg7326Gln); TTN c.8749A>C (p.Thr2917Pro); ACTN2 c.683T>C (p.Met228Thr); and OBSCN c.13475T>G (p.Leu4492Arg). The novel variant ACTN2 c.683T>C (p.Met228Thr), located in the actin-binding domain, proved to be the only mutation fully

cosegregating with the cardiomyopathic trait in 18 additional family members (of whom 11 clinically affected). ACTN2 c.683T>C (p.Met228Thr) was absent in 570 alleles of healthy controls and in 1000 Genomes Project and was labeled as Damaging by in silico analysis using polymorphism phenotyping v2, as Deleterious by sorts intolerant from tolerant, and as Disease-Causing by Mutation Taster.

CONCLUSIONS: A targeted next-generation sequencing approach allowed the identification of a novel ACTN2 variant associated with midapical HCM and juvenile onset of atrial fibrillation, emphasizing the potential of such approach in HCM diagnostic screening.

22. Eur Heart J. 2014 Oct 14;35(39):2733-79. doi: 10.1093/eurheartj/ehu284. Epub 2014 Aug 29.

2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC).

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Comment in Heart. 2015 Apr;101(7):506-8. Rev Esp Cardiol (Engl Ed). 2015 Jan;68(1):4-9.

23. Circulation. 2014 Aug 5;130(6):484-95. doi: 10.1161/CIRCULATIONAHA.113.007094.

Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy.

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BACKGROUND: Hypertrophic cardiomyopathy (HCM) is the most common cause of sudden death in the young, although not all patients eligible for sudden death prevention with an implantable cardioverter-defibrillator are identified. Contrast-enhanced cardiovascular magnetic resonance with late gadolinium enhancement (LGE) has emerged as an in vivo marker of myocardial fibrosis, although its role in stratifying sudden death risk in subgroups of HCM patients remains incompletely understood.

METHODS AND RESULTS: We assessed the relation between LGE and cardiovascular outcomes in 1293 HCM patients referred for cardiovascular magnetic resonance and followed up for a median of 3.3 years. Sudden cardiac death (SCD) events (including appropriate defibrillator interventions) occurred in 37 patients (3%). A continuous relationship was evident between LGE by percent left ventricular mass and SCD event risk in HCM patients (P=0.001). Extent of LGE was associated with an increased risk of SCD events (adjusted hazard ratio, 1.46/10% increase in LGE; P=0.002), even after adjustment for other relevant disease variables. LGE of ≥15% of LV mass demonstrated a 2-fold increase in SCD event risk in those patients otherwise considered to be at lower risk, with an estimated likelihood for SCD events of 6% at 5 years. Performance of the SCD event risk model wasenhanced by LGE (net reclassification index, 12.9%; 95% confidence interval, 0.3-38.3). Absence of LGE was associated with lower risk for SCD events (adjusted hazard ratio, 0.39; P=0.02). Extent of LGE also predicted the development of end-stage HCM with systolic dysfunction (adjusted hazard ratio, 1.80/10% increase in LGE; P<0.03).

CONCLUSIONS: Extensive LGE measured by quantitative contrast enhanced CMR provides additional information for assessing SCD event risk among HCM patients, particularly patients otherwise judged to be at low risk.

24. Am J Cardiol. 2014 Sep 1;114(5):769-76. doi: 10.1016/j.amjcard.2014.05.065. Epub 2014 Jun 19.

Significance of sarcomere gene mutations analysis in the end-stage phase of hypertrophic cardiomyopathy.

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End-stage hypertrophic cardiomyopathy (ES-HC) has an ominous prognosis. Whether genotype can influence ES-HC occurrence is unresolved. We assessed the spectrum and clinical correlates of HC-associated mutations in a large multicenter cohort with end-stage ES-HC. Sequencing analysis of 8 sarcomere genes (MYH7, MYBPC3, TNNI3, TNNT2, TPM1, MYL2, MYL3, and ACTC1) and 2 metabolic genes (PRKAG2 and LAMP2) was performed in 156 ES-HC patients with left ventricular (LV) ejection fraction (EF) <50%. A comparison among mutated and negative ES-HC patients and a reference cohort of 181 HC patients with preserved LVEF was performed. Overall, 131 mutations (36 novel) were identified in 104 ES-HC patients (67%) predominantly affecting MYH7 and MYBPC3 (80%). Complex genotypes with double or triple mutations were present in 13% compared with 5% of the reference cohort ($p = 0.013$). The distribution of mutations was otherwise indistinguishable in the 2 groups. Among ES-HC patients, those presenting at first evaluation before the age of 20 had a 30% prevalence of complex genotypes compared with 19% and 21% in the subgroups aged 20 to 59 and ≥60 years ($p = 0.003$). MYBPC3 mutation carriers with ES-HC were older than patients with MYH7, other single mutations, or multiple mutations (median 41 vs 16, 26, and 28 years, $p \leq 0.001$). Outcome of ES-HC patients was severe irrespective of genotype. In conclusion, the ES phase of HC

is associated with a variable genetic substrate, not distinguishable from that of patients with HC and preserved EF, except for a higher frequency of complex genotypes with double or triple mutations of sarcomere genes.

25. Am J Cardiol. 2013 Oct 15;112(8):1190-6. doi: 10.1016/j.amjcard.2013.06.018. Epub 2013 Jul 19.

Prognostic value of N-terminal pro-brain natriuretic Peptide in outpatients with hypertrophic cardiomyopathy.

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In hypertrophic cardiomyopathy, the plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) correlate with functional capacity. However, their prognostic relevance remains unresolved. We followed up 183 stable outpatients with hypertrophic cardiomyopathy (age 50 ± 17 years, 64% men) for 3.9 ± 2.8 years after NT-proBNP measurement. The primary end point included cardiovascular death, heart transplantation, resuscitated cardiac arrest, and appropriate implantable cardioverter-defibrillator intervention. The secondary end point (SE) included heart failure-related death or hospitalization, progression to end-stage disease, and stroke. The median NT-proBNP level was 615 pg/ml (intertertile range 310 to 1,025). The incidence of the primary end point in the lower, middle, and upper tertiles was 0%, 1.3%, and 2.1% annually, respectively (overall p = 0.01). On multivariate analysis, the only independent predictors of the primary end point were NT-proBNP (hazard ratio for log-transformed values 5.8, 95% confidence interval 1.07 to 31.6; p = 0.04) and a restrictive left ventricular filling pattern (hazard ratio 5.19, 95% confidence interval 1.3 to 21.9; p = 0.02). The NT-proBNP cutoff value of 810 pg/ml had the best sensitivity for the primary end point (88%), but the specificity was low (61%). The incidence of the SE in the lower, middle, and upper NT-proBNP tertiles was 4.6%, 12.0%, and 11.2% annually, respectively (overall p = 0.001). AnNT-proBNP level of <310 pg/ml was associated with a 75% reduction in the rate of SE compared with a level of ≥310 pg/ml (hazard ratio 0.25, 95% confidence interval 0.11 to 0.57; p = 0.001), independent of age, left ventricular outflow tract obstruction, or atrial fibrillation. In conclusion, in stable outpatients with hypertrophic cardiomyopathy, plasma NT-proBNP proved a powerful independent predictor of death and heart failure-related events. Although the positive predictive accuracy of an elevated NT-proBNP level was modest, low values reflected true clinical stability, suggesting the possibility of avoiding or postponing aggressive treatment options.

26. Eur J Heart Fail. 2013 Dec;15(12):1363-73. doi: 10.1093/eurjhf/hft104. Epub 2013 Jun 30.

Coronary microvascular dysfunction is an early feature of cardiac involvement in patients with Anderson-Fabry disease.

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AIMS: Male patients with Anderson-Fabry disease (AFD) often exhibit cardiac involvement, characterized by LV hypertrophy (LVH), associated with severe coronary microvascular dysfunction (CMD). Whether CMD is present in patients without LVH, particularly when female, remains unresolved. The aim of the study was to investigate the presence of CMD by positron emission tomography (PET) in AFD patients of both genders, with and without evidence of LVH.

METHODS AND RESULTS: We assessed myocardial blood flow following dipyridamole infusion (Dip-MBF) with 13N-labelled ammonia by PET in 30 AFD patients (age 51 ± 13 years; 18 females) and in 24 healthy controls. LVH was defined as echocardiographic maximal LV wall thickness ≥13 mm. LVH was present in 67% of patients (n = 20; 10 males and 10 females). Dip-MBF was reduced in all patients compared with controls (1.8 ± 0.5 and 3.2 ± 0.5 mL/min/g, respectively, P <0.001). For both genders, flow impairment was most severe in patients with LVH (1.4 ± 0.5 mL/min/g in males and 1.9 ± 0.5 mL/min/g in females), but was also evident in those without LVH (1.8 ± 0.3 mL/min/g in males and 2.1 ± 0.4 mL/min/g in females; overall P = 0.064 vs. patients with LVH). Analysis of variance (ANOVA) for the 17 LV segments showed marked regional heterogeneity of MBF in AFD (F = 4.46, P < 0.01), with prevalent hypoperfusion of the apical region. Conversely, controls showed homogeneous LV perfusion (F = 1.25, P = 0.23).

CONCLUSIONS: Coronary microvascular function is markedly impaired in AFD patients irrespective of LVH and gender. CMD may represent the only sign of cardiac involvement in AFD patients, with potentially important implications for clinical management.

27. J Am Coll Cardiol. 2013 Jul 30;62(5):449-57. doi: 10.1016/j.jacc.2013.03.062. Epub 2013 Apr 30.

Obesity and its association to phenotype and clinical course in hypertrophic cardiomyopathy.

Olivotto I(1), Maron BJ, Tomberli B, Appelbaum E, Salton C, Haas TS, Gibson CM, Nistri S, Servettini E, Chan RH, Udelson JE, Lesser JR, Cecchi F, Manning WJ, Maron MS.

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Comment in J Am Coll Cardiol. 2013 Jul 30;62(5):458-9.

OBJECTIVES: This study sought to assess the impact of body mass index (BMI) on cardiac phenotypic and clinical course in a multicenter hypertrophic cardiomyopathy (HCM) cohort.

BACKGROUND: It is unresolved whether clinical variables promoting left ventricular (LV) hypertrophy in the general population, such as obesity, may influence cardiac phenotypic and clinical course in patients with HCM. METHODS: In 275 adult HCM patients (age 48 ± 14 years; 70% male), we assessed the relation of BMI to LV mass, determined by cardiovascular magnetic resonance (CMR) and heart failure progression.

RESULTS: At multivariate analysis, BMI proved independently associated with the magnitude of hypertrophy: pre-obese and obese HCM patients (BMI 25 to 30 kg/m(2) and >30 kg/m(2), respectively) showed a 65% and 310% increased likelihood of an LV mass in the highest quartile (>120 g/m(2)), compared with normal weight patients (BMI <25 kg/m(2); hazard ratio [HR]: 1.65; 95% confidence interval [CI]: 0.73 to 3.74, p = 0.22 and 3.1; 95% CI: 1.42 to 6.86, p = 0.004, respectively). Other features associated with LV mass >120 g/m(2) were LV outflow obstruction (HR: 4.9; 95% CI: 2.4 to 9.8; p < 0.001), systemic hypertension (HR: 2.2; 95% CI: 1.1 to 4.5; p = 0.026), and male sex (HR: 2.1; 95% CI: 0.9 to 4.7; p = 0.083). During a median follow-up of 3.7 years (interquartile range: 2.5 to 5.3), obese patients showed an HR of 3.6 (95% CI: 1.2 to 10.7, p = 0.02) for developing New York Heart Association (NYHA) functional class III to IV symptoms compared to nonobese patients, independent of outflow obstruction. Noticeably, the proportion of patients in NYHA functional class III at the end of follow-up was 13% among obese patients, compared with 6% among those of normal weight (p = 0.03).

CONCLUSIONS: In HCM patients, extrinsic factors such as obesity are independently associated with increase in LV mass and may dictate progression of heart failure symptoms.

28. PLoS One. 2013;8(3):e59206. doi: 10.1371/journal.pone.0059206. Epub 2013 Mar 19.

Molecular modeling of disease causing mutations in domain C1 of cMyBP-C.

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Cardiac myosin binding protein-C (cMyBP-C) is a multi-domain (C0-C10) protein that regulates heart muscle contraction through interaction with myosin, actin and other sarcomeric proteins. Several mutations of this protein cause familial hypertrophic cardiomyopathy (HCM). Domain C1 of cMyBP-C plays a central role in protein interactions with actin and myosin. Here, we studied structure-function relationship of three disease causing mutations, Arg177His, Ala216Thr and Glu258Lys of the domain C1 using computational biology techniques with its available X-ray crystal structure. The results suggest that each mutation could affect structural properties of the domain C1, and hence it's structural integrity through modifying intra-molecular arrangements in a distinct mode. The mutations also change surface charge distributions, which could impact the binding of C1 with other sarcomeric proteins thereby affecting contractile function. These structural consequences of the C1 mutants could be valuable to understand the molecular mechanisms for the disease.

29. JIMD Rep. 2013;8:51-6. doi: 10.1007/8904_2012_160. Epub 2012 Jul 14.

Recommendations on reintroduction of agalsidase Beta for patients with fabry disease in europe, following a period of shortage.

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The interruption of the manufacturing process of agalsidase beta has led to a worldwide shortage of this drug. In the EU, nearly all patients initially reduced their agalsidase beta dose, and many of these switched to agalsidase alfa (Replagal Shire HGT). The clinical consequences of this period of drug shortage need to be further evaluated. A gradual increase of agalsidase beta supply is now expected. This implies that patients could resume or even commence agalsidase beta treatment. Guidance for prioritization of patients is needed to support equitable distribution of agalsidase beta to EU member states. To achieve this, in absence of level I clinical evidence, a draft consensus proposal was initiated and distributed. No full consensus was achieved, as there is disagreement regarding the indications for switching patients from agalsidase alfa to agalsidase beta. Some physicians support the concept that the 1.0 mg/kg EOW dose of agalsidase beta is more effective than agalsidase alfa at 0.2 mg/kg EOW, while others believe that at recommended dose, the preparations are equivalent. In light of these difficulties and the uncertainties with respect to supply of agalsidase beta, recommendations were agreed upon by a subgroup of physicians. These current recommendations focus on prioritization of criteria indicative of disease progression.

30. Glob Cardiol Sci Pract. 2013 Nov 1;2013(3):243-8. doi: 10.5339/gcsp.2013.31.eCollection 2013.

Hypertrophic cardiomyopathy: The need for randomized trials.

Olivotto I, Tomberli B, Spoladore R, Mugelli A, Cecchi F, Camici PG.

Hypertrophic cardiomyopathy (HCM) is a complex cardiac condition characterized by variable degrees of asymmetric left ventricular (LV) hypertrophy, generally associated with mutations in sarcomere protein genes. While generally perceived as rare, HCM is the most common genetic heart disease with over one million affected individuals in Europe alone and represents a prevalent cause of sudden cardiac death in the young. To date, HCM remains an orphan disease, as recommended treatment strategies are based on the empirical use of old drugs with little evidence supporting their clinical benefit in this context. In the six decades since the original description of the disease, less than fifty pharmacological studies have been performed in HCM patients, enrolling little over 2,000 HCM patients, mostly comprising small non-randomized cohorts. No specific agent has been convincingly shown to affect outcome, and critical issues such as prevention of myocardial energy depletion, microvascular ischemia, progressive myocardial fibrosis and the peculiar mechanisms of arrhythmogenesis in HCM still need to be addressed in a systematic fashion. However, there is increasing evidence that a variety of drugs may counter the effects of sarcomere protein mutations and the resulting pathophysiological abnormalities at the molecular, cellular and organ level. Following major advances in our understanding of HCM and increasing opportunities for networking among large international referral centres, the opportunity now exists to identify potentially effective treatments and implement adequately designed pharmacological trials, with the ultimate

aim to impact the natural course of the disease, alleviate symptoms and improve quality of life in our patients.

31. J Cardiovasc Transl Res. 2013 Feb;6(1):65-80. doi: 10.1007/s12265-012-9425-0.

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Early results of sarcomeric gene screening from the Egyptian National BA-HCMProgram.

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Erratum in J Cardiovasc Transl Res. 2013 Aug;6(4):663. Ayad, Maha S [corrected to Saber-Ayad, Maha].

The present study comprised sarcomeric genotyping of the three most commonly involved sarcomeric genes: MYBPC3, MYH7, and TNNT2 in 192 unrelated Egyptian hypertrophic cardiomyopathy (HCM) index patients. Mutations were detected in 40 % of cases. Presence of positive family history was significantly (p=0.002) associated with a higher genetic positive yield (49/78, 62.8 %). The majority of the detected mutations in the three sarcomeric genes were novel (40/62, 65 %) and mostly private (47/62, 77 %). Single nucleotide substitution was the most frequently detected mutation type (51/62, 82 %). Over three quarters of these substitutions (21/27, 78 %) involved CpG dinucleotide sites and resulted from C>T or G>A transition in the three analyzed genes, highlighting the significance of CpG high mutability within the sarcomeric genes examined. This study could aid in global comparative studies in different ethnic populations and constitutes animportant step in the evolution of the integrated clinical, translational, and basic science HCM program.

32. Circ Heart Fail. 2012 Jul 1;5(4):535-46. doi: 10.1161/CIRCHEARTFAILURE.112.967026.

Patterns of disease progression in hypertrophic cardiomyopathy: an individualized approach to clinical staging.

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33. Am J Cardiol. 2012 Sep 1;110(5):715-9. doi: 10.1016/j.amjcard.2012.04.051. Epub 2012 May 24.

β Blockers for prevention of exercise-induced left ventricular outflow tract obstruction in patients with hypertrophic cardiomyopathy.

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Whether treatment with β blockers (BBs) is of benefit to patients with hypertrophic cardiomyopathy (HC) and provocable outflow obstruction (with none or with only mild heart failure symptoms) is largely unresolved. Thus, we prospectively studied 27 patients with HC (age 36 ± 15 years; 81% men) with New York Heart Association class I or II, without obstruction at rest, but with exercise-induced left ventricular outflow tract (LVOT) gradient of ≥ 30 mm Hg. Patients underwent exercise echocardiography at baseline and after treatment with nadolol (n = 18; 40 to 80 mg/day) or bisoprolol (n = 9; 5 to 10 mg/day), according to a prespecified protocol. Without the BBs, the postexercise LVOT gradient was 87 ± 29 mm Hg and >50 mm Hg in 25 patients (93%). After a 12 ± 4-month period of BB treatment, the postexercise LVOT gradient had decreased to 36 ± 22 mm Hg (p <0.001) and was virtually abolished (to 0 or <30 mm Hg) in 14 patients (52%), substantially blunted (≥ 20 mm Hg reduction) in 9 (33%), and unchanged in only 4 (15%). Severe postexercise obstruction (range 58 to 80 mm Hg) persisted in 6 patients (22% compared to 93% without BBs; p <0.001). Nonresponders (residual postexercise gradient of ≥ 30 mm Hg with BBs) were characterized by an increased body mass index (hazard ratio 2.03/1 kg/m(2), 95% confidence interval 1.2 to 3.4; p <0.05). In conclusion, in patients with HC with mild or no symptoms, treatment with BBs can prevent the development of LVOT obstruction triggered by physiologic exercise. These findings provide a rationale for the novel strategy of early prophylactic pharmacologic treatment with standard, well-tolerated doses of BBs in physically active patients with provocable gradients, aimed at effective prevention of the hemodynamic burden associated with dynamic obstruction.

34. G Ital Cardiol (Rome). 2012 Apr;13(4):297-303. doi: 10.1714/1056.11562.

[Management of refractory symptoms in hypertrophic cardiomyopathy withrestrictive pathophysiology: novel perspectives for ranolazine].[Article in Italian]

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Comment in G Ital Cardiol (Rome). 2012 Dec;13(12):861; author's reply p.861.

The management of patients with hypertrophic cardiomyopathy (HCM) and refractory symptoms due to massive hypertrophy and severe diastolic dysfunction represents a real challenge for the clinical cardiologist. Such patients often require novel therapeutic approaches, both invasive and

pharmacological, involving multidisciplinary teamwork; however, the implementation of potentially viable treatment options is hindered by lack of disease-specific evidence. We report the case of a young woman with severe HCM and restrictive physiology, who underwent extensive myectomy via the transaortic and transapical approach, followed by biventricular pacing for cardiac resynchronization, with significant but incomplete symptomatic improvement. The subsequent introduction of ranolazine, based on promising preclinical data, has led to an excellent final result. An ongoing randomized clinical trial is currently testing the efficacy of ranolazine in symptomatic HCM.

35. Int J Cardiol. 2013 Aug 10;167(3):1038-45. doi: 10.1016/j.ijcard.2012.03.074. Epub 2012 Mar 30.

Relationship of ECG findings to phenotypic expression in patients with hypertrophic cardiomyopathy: a cardiac magnetic resonance study.

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BACKGROUND: The 12-lead electrocardiogram (ECG) is considered an essential screening tool for hypertrophic cardiomyopathy (HCM). A vast array of ECG abnormalities has been described in HCM, although their relationship to left ventricle (LV) morphology and degree of hypertrophy appears elusive. Aim of this study was to assess the relationship of ECG patterns with the HCM phenotype assessed according to the novel opportunities offered by cardiac magnetic imaging (CMR).

METHODS: CMR and 12-lead ECG were performed in 257 HCM patients. Severity of ECG abnormalities was defined by the sum of 9 criteria: abnormal cardiac rhythm, QRS duration ≥ 100 ms, Romhilt-Estes score ≥ 5, fascicular block (LAHB) and/or bundle-branch block (LBBB or RBBB), ST-T abnormalities, ST-T segment elevation ≥ 0.2 mV, prolonged QTc interval, pathological Q waves, absence of normal Q wave. Four ECG groups were identified: normal (0 criteria); mildly abnormal (1-3 criteria); moderately abnormal (4-6 criteria); markedly abnormal (7-9 criteria). RESULTS: There was a direct relationship between severity of ECG abnormalities and HCM phenotype. LV mass index was normal in most patients with normal ECG and progressively increased with each class of ECG score, from 70.9 ± 18.6g/m(2) in patients with normal ECG to 107.1 ± 55.1g/m(2) among those with markedly abnormal ECG (p=<0.0001). Likewise, the prevalence and extent of late gadolinium enhancement (LGE) increased significantly with the ECG score, from 37% in patients with normal ECG to 93% in patients with markedly abnormal ECG (overall p=0.0012). A normal ECG had a negative predictive accuracy of 96% for markedly increased LV mass (>91 g/m(2) for men and >69 g/m(2) for women), and of 100% for maximum LV thickness ≥ 30 mm.

CONCLUSIONS: In a large HCM cohort, the number and severity of ECG abnormalities were directly related to phenotypic expression as revealed by CMR. Although false negative ECG findings remain a challenge in population screenings for HCM, a normal ECG proved effective in ruling out severe LV hypertrophy, suggesting potential implications for long-term follow-up of HCM patients and family members. A simple score for quantification of ECG abnormalities in HCM patients is proposed.

36. Recenti Prog Med. 2011 Dec;102(12):486-93. doi: 10.1701/998.10862.

[Clinical relevance of genetic testing in hypertrophic cardiomyopathy].

[Article in Italian]

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More than two decades have elapsed since the discovery that sarcomere gene defects cause familial hypertrophic cardiomyopathy (HCM). Since then, genetic testing in HCM has developed, and become an important tool in clinical practice for diagnosis and prognosis overall in the Western countries. However its practical benefits are still understimated and clinicians often question about cost-effectiveness of genic testing in HCM patients and their families. This resistance is in contrast with considerable evidence supporting the role of genetics in tailoring management for HCM patients. Several current clinical uses of genetic testing in HCM, ranging from diagnosis in ambiguous situations, identification of disease phenocopies and HCM complex genotypes and confirmation of inherited disease in family members are reviewed. In the near future it is hoped that next generation sequencing will provide further diffusion of genetic testing in HCM and improvement in care.

37. Glob Cardiol Sci Pract. 2012 Jul 3;2012(1):9. doi: 10.5339/gcsp.2012.9. eCollection 2012.

Pattern and degree of left ventricular remodeling following a tailored surgical approach for hypertrophic obstructive cardiomyopathy.

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Background The role of a tailored surgical approach for hypertrophic cardiomyopathy (HCM) on regional ventricular remodelling remains unknown. The aims of this study were to evaluate the pattern, extent and functional impact of regional ventricular remodelling after a tailored surgical approach. Methods From 2005 to 2008, 44 patients with obstructive HCM underwent tailored surgical intervention. Of those, 14 were ineligible for cardiac magnetic resonance (CMR) studies. From the remainder, 14 unselected patients (42±12 years) underwent pre- and post-operative CMR

studies at a median 12 months post-operatively (range 4-37 months). Regional changes in left ventricular (LV) thickness as well as global LV function following surgery were assessed using CMR Tools (London, UK). Results Pre-operative mean echocardiographic septal thickness was 21±4 mm and mean LV outflow gradient was 69±32 mmHg. Following surgery, there was a significant degree of regional regression of LV thickness in all segments of the LV, ranging from 16% in the antero-lateral midventricular segment to 41% in the anterior basal segment. Wall thickening was significantly increased in basal segments but showed no significant change in the midventricular or apical segments. Globally, mean indexed LV mass decreased significantly after surgery (120±29g/m2 versus 154±36g/m2; p<0.001). There was a trend for increased indexed LV end-diastolic volume (70±13 mL versus 65±11 mL; p=0.16) with a normalization of LV ejection fraction (68±7% versus 75±9%; p<0.01). Conclusion Following a tailored surgical relief of outflow obstruction for HCM, there is a marked regional reverse LV remodelling. These changes could have a significant impact on overall ventricular dynamics and function.

38. Glob Cardiol Sci Pract. 2012 Jul 3;2012(1):4. doi: 10.5339/gcsp.2012.4. eCollection 2012.

Clinical and molecular classification of cardiomyopathies.

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The term "cardiomyopathies" was used for the first time 55 years ago, in 1957. Since then awareness and knowledge of this important and complex group of heart muscle diseases have improved substantially. Over these past five decades a large number of definitions, nomenclature and schemes, have been advanced by experts and consensus panel, which reflect the fast and continued advance of the scientific understanding in the field. Cardiomyopathies are a heterogeneous groupof inherited myocardial diseases, which represent an important cause of disability and adverse outcome. Although considered rare diseases, the overall estimated prevalence of all cardiomyopathies is at least 3% in the general population worldwide. Furthermore, their recognition is increasing due to advances in imaging techniques and greater awareness in both the public and medical community. Cardiomyopathies represent an ideal translational model of integration between basic and clinical sciences. A multidisciplinary approach is therefore essential in order to ensure their correct diagnosis and management. In the present work, we aim to provide a concise overview of the historical background, genetic and phenotypic spectrum and evolving concepts leading to the various attempts of cardiomyopathy classifications produced over the decades.

39. G Ital Cardiol (Rome). 2011 Dec;12(12):815-23. doi: 10.1714/996.10826.

[Disease progression and systolic dysfunction in patients with hypertrophic cardiomyopathy: genetic basis, pathophysiology and clinical presentation]. [Article in Italian]

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Progressive heart failure associated with left ventricular remodeling and systo-diastolic dysfunction is one of the most severe complications of hypertrophic cardiomyopathy (HCM). Such condition, for the lack of a better term, is referred to as end-stage (ES) HCM. During the last decade, we have begun to understand the mechanisms underlying progression from a hyperdynamic left ventricle to the striking patterns of ES. To date, different aspects of HCM progression remain obscure, including potential strategies for management and prevention. On the basis of recent evidence, it is appropriate to emphasize these aspects, which may be difficult to identify, particularly in the early stages when systolic function appears relatively preserved. Nevertheless, it is at these early stages that treatment may potentially interfere with the clinical evolution of HCM toward ES and heart failure. The possibility of early identification of patients at risk of ES progression may ultimately impact on the natural history of the disease in this challenging patient subgroup.

40. Am J Cardiol. 2012 Mar 1;109(5):718-23. doi: 10.1016/j.amjcard.2011.10.035. Epub 2011 Dec 10.

Hemodynamic progression and outcome of asymptomatic aortic stenosis in primary care.

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The prognostic relevance of a rapid rate of hemodynamic progression of aortic stenosis (AS) has been predominantly investigated in tertiary centers. We reviewed the clinical and echocardiographic data from 153 asymptomatic patients with AS (age 77 ± 9 years; 65% men), with normal left ventricular function and paired echocardiograms ≥4 months apart (mean 2.9 ± 2.1 years), evaluated in a nonreferral echocardiographic laboratory. The severity of AS was graded by the peak aortic velocity (Vmax) and progression was classified as slow or fast according to a cutoff value of 0.3 m/s increase annually. The end points were all-cause mortality and a composite of all-cause mortality and aortic valve replacement (AVR). At baseline, 135 patients (88%) had mild-to-moderate and 18 (12%) severe AS. Of the 153 patients, 49 (32%) showed fast progression (0.61 ±0.32 m/s/yr) and 104 (68%) had slow progression (0.10 ± 0.16 m/s/yr). Among the144 patients (94%) with clinical follow-up data, 40 died and 48 underwent AVR. The mortality rate was greater than that of the general population (p <0.001). On multivariate analysis, the independent predictors of mortality were the yearly change in Vmax (hazard ratio [HR] 13.352 per m/s increase, 95% confidence interval [CI] 5.136 to 34.713, p <0.001) and age (HR 1.122 per year, 95% CI 1.0728 to 1.735, p <0.001). The predictors of the composite end point of death and AVR were the yearly change in Vmax (HR 12.307, 95% CI 6.024 to 25.140, p <0.001) and Vmax on the initial echocardiogram (HR 2.684, 95% CI 1.921 to 3.750, p <0.001). In conclusion, primary care patients with asymptomatic AS are usually elderly and frequently develop rapid hemodynamic progression, which independently predicts, not only AVR, but also overall mortality.

41. Eur J Echocardiogr. 2011 Nov;12(11):826-33. doi: 10.1093/ejechocard/jer137. Epub 2011 Aug 30.

Determinants of echocardiographic left atrial volume: implications for normalcy.

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AIMS: The relative role of multiple determinants of left atrial volume index (LAVi) in athletes and non-athletes is not fully defined. Thus, we decided to prospectively assess the determinants of LAVi in healthy individuals and competitive athletes over a wide age range.
METHODS AND RESULTS: Four hundred and eighteen healthy individuals (mean age 41.7 ± 15.6 years, range 16-84, 65% males, 38% competitive athletes) underwent Doppler echocardiography including assessment of LAVi by the biplane area-length method and of left ventricular (LV) diastolic function including the ratio of early diastolic peak LV inflow velocity to peak myocardial early diastolic velocity (E/e'). Mean LAVi was 32.2 ± 9.0 mL/m(2) in the pooled population. LAVi was larger in athletes than in non-athletes (38.9 ± 9.6 mL/m(2) vs. 28.4 ± 5.8 mL/m(2), $P < 0.0001$). In the pooled population a stepwise multiple linear regression analysis identified LV end-diastolic volume index (LVEDVi) ($\beta = 0.378$, $P < 0.0001$), LV mass index (LVMi) ($\beta = 0.260$, $P < 0.0001$), competitive sport activity ($\beta = 0.258$, $P < 0.0001$), and age ($\beta = 0.222$, $P < 0.0001$) as independent determinants of LAVi (model $R(2) = 0.54$, $P < 0.0001$). By separate analyses, although LVEDVi, age, and LVMi were predictors of LAVi in both groups, body mass index and the E/e' ratio were additional predictors of LAVi only in non-athletes.
CONCLUSIONS: In healthy individuals LV size, competitive sport, age, and LV mass are independent determinants of LAVi. Body mass index and the E/e' ratio affect LAVi only in non-athletes. These findings may have practical implications when assessing normalcy of LA size in the clinical setting.

42. J Am Coll Cardiol. 2011 Aug 16;58(8):839-48. doi: 10.1016/j.jacc.2011.05.018.

Microvascular function is selectively impaired in patients with hypertrophic cardiomyopathy and sarcomere myofilament gene mutations.

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OBJECTIVES: The purpose of this study was to assess myocardial blood flow (MBF)using positron emission tomography in patients with hypertrophic cardiomyopathy (HCM) according to genetic status.
BACKGROUND: Coronary microvascular dysfunction is an important feature of HCM, associated with ventricular remodeling and heart failure. We recently demonstrated the increased prevalence of systolic dysfunction in patients with HCM with sarcomere myofilament gene mutations and postulated an association between genetic status and coronary microvascular dysfunction.
METHODS: Maximum MBF (intravenous dipyridamole, 0.56 mg/kg; Dip-MBF) was measured using (13)N-labeled ammonia in 61 patients with HCM (age 38 ± 14 years), genotyped by automatic DNA sequencing of 8 myofilament-encoding genes (myosin-binding protein C, beta-myosin heavy chain, regulatory and essential light chains, troponin T, troponin I, troponin C, alpha-tropomyosin, and alpha-actin). In 35 patients, cardiac magnetic resonance imaging was performed.

RESULTS: Fifty-three mutations were identified in 42 of the 61 patients (genotype positive; 69%). Despite similar clinical profiles, genotype-positive patients with HCM showed substantially lower Dip-MBF compared with that of genotype-negative patients (1.7 ± 0.6 ml/min/g vs. 2.4 ± 1.2 ml/min/g; $p < 0.02$). A Dip-MBF <1.5 ml/min/g had 81% positive predictive value for genotype-positive status and implied a 3.5-fold independent increase in likelihood of carrying myofilament gene mutations (hazard ratio: 3.52; 95% confidence interval: 1.05 to 11.7; $p = 0.04$). At cardiac magnetic resonance imaging, the prevalence of late gadolinium enhancement was greater in genotype-positive patients (22 of 23 [96%] compared with 8 of 12 [67%] genotype-negative patients; $p = 0.038$).
CONCLUSIONS: Patients with HCM with sarcomere myofilament mutations are characterized by more severe impairment of microvascular function and increased prevalence of myocardial fibrosis, compared with genotype-negative individuals. These findings suggest a direct link between sarcomere gene mutations and adverse remodeling of the microcirculation in HCM, accounting for the increased long-term prevalence of ventricular dysfunction and heart failure in genotype-positive patients.

43. J Am Coll Cardiol. 2011 Mar 1;57(9):1093-9. doi: 10.1016/j.jacc.2010.11.018.

Cardiovascular events in patients with fabry disease natural history data from the fabry registry.

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OBJECTIVES: These analyses were designed to determine the incidence of major cardiovascular (CV) events and the natural history of CV complications in patients with Fabry disease.
BACKGROUND: Fabry disease, a genetic disorder caused by deficiency of alpha-galactosidase A activity, is associated with CV dysfunction.
METHODS: Major CV events (myocardial infarction, heart failure, or cardiac-related death) were analyzed in 2,869 Fabry Registry patients during the natural history period (i.e., before enzyme replacement therapy or among patients who never received therapy). Multivariate logistic regression analyses were performed to identify significant predictors of CV events.
RESULTS: Eighty-three of 1,424 men (5.8%) and 54 of 1,445 women (3.7%) experienced CV events at mean ages of 45 and 54 years, respectively. Heart failure was the most common first CV event, reported by 50 men (3.5%) and 33 women (2.3%). Hypertension and left ventricular hypertrophy were the risk factors most strongly associated with CV events. When these parameters were used as covariates in logistic regression analyses, the odds ratio (OR) for hypertension in men was 7.8 (95% confidence interval [CI]: 2.1 to 28.6, $p = 0.0019$), and the OR for hypertension in women was 4.5 (95% CI: 1.6 to 12.3, $p = 0.0037$). The OR for left ventricular hypertrophy was 4.8 in men (95% CI: 1.03 to 22.2, $p = 0.0463$) and 8.2 in women (95% CI: 2.6 to 26.0, $p = 0.0003$).
CONCLUSIONS: Major CV events occurred in approximately 5% of Fabry Registry patients during the natural history period. All patients with Fabry disease should be monitored for possible CV risk factors, particularly hypertension and left ventricular hypertrophy.

44. Eur Heart J. 2011 May;32(9):1114-20. doi: 10.1093/eurheartj/ehr021. Epub 2011 Feb 22.

Prevalence and clinical correlates of QT prolongation in patients with hypertrophic cardiomyopathy.

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AIMS: Congenital or acquired QT prolongation is a risk factor for life-threatening arrhythmias. In patients with hypertrophic cardiomyopathy (HCM), the QT interval may be intrinsically prolonged. However, the prevalence, cause, and significance of QT prolongation among patients with HCM are unknown.
METHODS AND RESULTS: After exclusion of patients on QT-prolonging drugs, a blinded, retrospective analysis of electrocardiograms, echocardiograms, and genotype status in 479 unrelated patients with HCM [201 females, age at diagnosis 41 ± 18 years, maximal left ventricular wall thickness (MLVWT) 22 ± 6 mm] from two independent centres was performed. The mean QTc was 440 ± 28 ms. The QTc exceeded 480 ms in 13% of patients. Age, gender, family history of HCM or sudden cardiac arrest, and genotype status had no association with QTc. Patients with a QTc over 480 ms were more symptomatic at diagnosis ($P < 0.001$), had a higher MLVWT ($P = 0.03$), were more obstructive ($P < 0.001$), and were more likely to have undergone septal reduction therapy ($P = 0.02$). There was a weak but significant direct linear relationship between QTc and peak outflow gradient ($r(2) = 0.05$, $P < 0.0001$).
CONCLUSIONS: Compared with <1 in 200 otherwise healthy adults, QT prolongation (QTc > 480 ms) was present in 1 out of 8 patients with HCM. The QTc was partly reflective of the degree of cardiac hypertrophy and left ventricular outflow tract obstruction. Because of its pro-arrhythmic potential and its potential relevance to management and risk stratification, routine QTc assessment should be performed in patients with HCM, particularly when concomitant use of QT-prolonging medications is considered.

45. G Ital Cardiol (Rome). 2010 Jul-Aug;11(7-8):566-72.

[Cardiological follow-up in patients with Fabry disease]. [Article in Italian]

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Fabry disease is a rare tesaurismosis due to a deficit of the lysosomal enzyme activity of alpha-galactosidase, needed for the normal catabolism of globotriaosylceramides (GL3). Fabry cardiac involvement has several clinical manifestations: concentric left ventricular hypertrophy without left ventricular dilation and severe loss of left ventricular systolic function, mitral and aortic valvulopathy, disorders of the atrioventricular conduction or repolarization, and compromised diastolic function. Differentiating Fabry disease from similar conditions is often quite straightforward, e.g., cardiac amyloidosis is often associated with low electrocardiographic voltages, and systemic symptoms are usually associated with hemochromatosis and sarcoidosis. However, sometimes second-level (genetic analysis, alpha-galactosidase levels) or invasive investigations are required, which can include endomyocardial biopsy. Diagnostic imaging techniques have been described, but they lack specificity. Echocardiographic imaging with tissue Doppler analysis and/or strain rate analysis can allow diagnosis of Fabry disease even before left ventricular hypertrophy becomes apparent. This review illustrates the techniques for staging cardiac involvement and damage in Fabry disease and for the long-term follow-up of Fabry patients with or without cardiac

involvement. Careful cardiac monitoring is especially important in elderly female carriers, who often develop renal disorders and/or left ventricular hypertrophy as the only manifestations of their late Fabry disease. In some clinical series, Fabry disease was diagnosed in 12% of women with adult-onset hypertrophic cardiomyopathy. Cardiological problems and outcomes of enzyme replacement therapy, associated with or without other cardiological treatments, are also discussed.

46. Am J Cardiol. 2010 Nov 1;106(9):1301-6. doi: 10.1016/j.amjcard.2010.06.057. Epub 2010 Sep 21.

Timing and significance of exercise-induced left ventricular outflow tract pressure gradients in hypertrophic cardiomyopathy.

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Comment in Am J Cardiol. 2011 Apr 1;107(7):1101-2; author reply 1102.

The relation of exercise-induced left ventricular (LV) outflow tract obstruction to functional capacity in hypertrophic cardiomyopathy (HC) is incompletely defined. Thus, we assessed the patterns of onset of physiologically provoked LV outflow gradients and exercise performance in 74 consecutive patients with HC (age 45 ± 16 years; 74% men) without LV outflow obstruction at rest. The subaortic gradients were measured serially using echocardiography in these 74 patients during maximum, symptom-limited, upright bicycle exercise testing. The time course of the provoked gradients and the relation to exercise performance were assessed. Of the 74 patients, 30 (41%) developed a dynamic LV outflow gradient of ≥30 mm Hg (mean 78 ± 37 mm Hg) during upright exercise testing that correlated highly with the gradients measured with the patients supine during the immediate recovery period ($R^2 = 0.97$). The 16 patients in whom outflow obstruction developed rapidly at low exercise levels (≤5 METs) had a significantly reduced exercise capacity (6.1 ± 1.3 vs 8.0 ± 1.6 METs; $p < 0.01$) compared to the other 14 patients in whom obstruction appeared later at greater exercise levels of >5 METs. The timing of the gradient onset was not predictable from the baseline clinical and echocardiographic features, peak exercise LV outflow tract gradient, or symptoms. In conclusion, in patients with HC without outflow obstruction at rest, the earlier onset of LV outflow tract gradients during physiologic exercise was associated with impaired exercise performance.
These findings have provided insights into the determinants of functional impairment in HC and support the potential value of exercise echocardiography in the clinical assessment of patients with HC.

47. Arthritis Care Res (Hoboken). 2011 Mar;63(3):390-5. doi: 10.1002/acr.20385. Epub 2010 Oct 27.

Distal extremity pain as a presenting feature of Fabry's disease.

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OBJECTIVE: Fabry's disease (FD) is an X-linked lysosomal storage disease. Distal extremity pain can be an early finding and renal, cardiac, and cerebrovascular complications may lead to complications and mortality. Treatment is now available for these patients, who may not be diagnosed correctly for years if the neuropathic nature of the pain is not recognized. The aim of our study was to describe early clinical features in a cohort of patients with FD and to emphasize the importance of distal extremity pain for early diagnosis.

METHODS: The medical charts of 35 patients with FD followed in a single center were reviewed. When data were incomplete, a detailed pain questionnaire was sent to patients. Nonresponders were contacted by telephone.
RESULTS: Distal extremity pain was present in the majority of cases (25 of 35). The mean age at diagnosis of FD was 43.5 years (range 5-77 years). Distal extremity pain was more prevalent in males than females and occurred mostly in childhood or adolescence. When present at onset, the disease progressed with subsequent organ system involvement. Misdiagnoses were frequent and included growing pains, juvenile idiopathic arthritis, connective tissue disease, and gout.
CONCLUSION: Clinical manifestations of FD, including episodes of severe pain in the feet and hands, often start in childhood. Distal extremity pain may be the only symptom for a considerable period of time. Patients may be wrongly labeled as having rheumatologic conditions, resulting in long diagnostic and therapeutic delays. Rheumatologists should be aware of the clinical aspects of FD and include it in the differential diagnosis of distal extremity pain in childhood and adolescence.

48. G Ital Cardiol (Rome). 2010 May;11(5):377-85.

[Clinical and genetic features of left ventricular noncompaction: a continuum in cardiomyopathies]. [Article in Italian]

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Isolated left ventricular non-compaction (LVNC) is a rare genetic form of cardiomyopathy (CM) characterized by prominent left ventricular wall trabeculation and intertrabecular recesses communicating with the ventricular cavity. Clinical signs are variable, ranging from lack of symptoms to severe manifestations including heart failure, sustained ventricular arrhythmias, cardioembolism and sudden death. The diagnosis of LVNC is frequently missed, due to limited awareness in the medical community. Contemporary diagnostic sensitivity has been enhanced by the introduction of specific morphologic criteria by high resolution echocardiography and cardiac magnetic resonance. As a consequence, LVNC has been diagnosed more frequently in association with other disorders such as congenital heart disease or genetic CM. The clinical relevance of regional non-compaction in the context of other cardiac diseases is still uncertain. Recent evidence points to an overlapping genetic background encompassing LVNC, hypertrophic and dilated CM, suggesting a continuum of disease associated with sarcomere protein gene mutations. This concept may prove relevant to the understanding of common pathogenetic mechanisms of CM and offer novel research opportunities.

49. J Cardiovasc Transl Res. 2009 Dec;2(4):510-7. doi: 10.1007/s12265-009-9153-2. Epub 2009 Nov 26.

The left ventricular outflow in hypertrophic cardiomyopathy: from structure to function.

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Left ventricular outflow tract obstruction (LVOTO) is one of the defining features of hypertrophic cardiomyopathy (HCM) and one of the main determinants of prognosis. Although the importance

of obstruction was recognized since the original description by Teare and Brock, its exact cause and methods for its relief are still being hotly debated. We believe that a rational approach to solving these issues depends on thorough understanding of the specific structure and functions of the left ventricular outflow tract (LVOT) in health and disease. There is now compelling evidence that the LVOT performs a series of vital sophisticated functions which are mediated by the design characteristics, structure, and biological properties of its component parts and that dysregulation of one or more of these functions results in obstruction and other abnormalities. We here review the integrated functions of the LVOT, its structural and functional relationships, with particular reference to its component parts (the major players) and their role in HCM. This knowledge is essential to evolve tailored restorative techniques for treating HCM.

50. J Cardiovasc Transl Res. 2009 Dec;2(4):452-61. doi: 10.1007/s12265-009-9142-5.Epub 2009 Nov 3.

Microvascular dysfunction, myocardial ischemia, and progression to heart failure in patients with hypertrophic cardiomyopathy.

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Microvascular dysfunction can be demonstrated in most patients with hypertrophic cardiomyopathy (HCM), both in the hypertrophied and nonhypertrophied myocardial walls, mostly due to intimal and medial hyperplasia of the intramural coronary arteries and subsequent lumen reduction. As a consequence, regional myocardial ischemia may be triggered by exercise, increased heart rate, or arrhythmias, in areas which are unable to increase myocardial blood flow. In patients with HCM, microvascular dysfunction leading to severe myocardial hypoperfusion during maximal hyperemia represents a strong predictor of unfavorable outcome, left ventricular remodeling with progressive wall thinning, left ventricular dysfunction, and heart failure. Accurate quantitative assessment of microvascular dysfunction and myocardial ischemia is not easily feasible in clinical practice. Although signs of inducible myocardial ischemia may be detected by electrocardiogram, echocardiography, or myocardial scintigraphy, the vasodilator response to dipyridamole by positron emission tomography is considered the method of choice for the assessment of maximal regional and global flow. Cardiac magnetic resonance provides further information, by late gadolinium enhancement (LGE), which may show areas where replacement fibrosis has occurred following microvascular ischemia and focal necrosis. LGE areas colocalize with severe regional microvascular dysfunction, are associated with increased prevalence of ventricular arrhythmias, and show more extensive distribution in the late stages of the disease, when heart failure is the dominant feature. The present review aims to provide a concise overview of the available evidence of microvascular dysfunction and ischemia eventually leading to disease progression and heart failure in HCM patients.

51. J Cardiovasc Transl Res. 2009 Dec;2(4):392-7. doi: 10.1007/s12265-009-9135-4.Epub 2009 Oct 20.

Looking for hypertrophic cardiomyopathy in the community: why is it important?

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Hypertrophic cardiomyopathy (HCM) is an epidemiologically relevant, worldwide spread condition which is frequently perceived as a rare disease. This misconception might be supported by some characteristics of HCM such as its incomplete penetrance and variable age at onset and by the fact that many patients remain asymptomatic for a long course of the disease and are thus unlikely to seek for medical evaluation. Multiple evidences suggest that early diagnosis of HCM is important, not only because it allows the patients to be addressed to appropriate diagnostic work-out and to adequate therapeutical options but because it may trigger the screening of family members with the potential of further, new diagnosis of HCM in previously unsuspected individuals. Increased awareness of the disease among physicians working in community-based hospitals and in outpatients facilities, and a facilitated communication and access to tertiary referral centers, will result into a wider knowledge of the spectrum of the disease, a better access to the state-of-the-art management options for patients, and to a more diffuse practice of genetic evaluation of HCM families.

52. J Cardiovasc Transl Res. 2009 Dec;2(4):349-67. doi: 10.1007/s12265-009-9137-2. Epub 2009 Oct 27.

The many faces of hypertrophic cardiomyopathy: from developmental biology to clinical practice.

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Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, characterized by complex pathophysiology, heterogeneous morphology, and variable clinical manifestations over time. Besides cardiac hypertrophy, the HCM phenotype is characterized by a host of manifestations, including mitral valve and subvalvar abnormalities, subaortic and mid-ventricular left ventricular (LV) obstruction, microvascular dysfunction, myocardial fibrosis, disarray, atrial remodeling, myocardial bridging of epicardial coronary arteries, LV apical aneurysms, and autonomic nervous system abnormalities. Such heterogeneous phenotype still lacks a comprehensive explanation, which cannot be accounted solely by genetic heterogeneity, despite the large number of genes and mutations involved. It is likely that pre-natal and acquired features deriving from the primary genetic defect interact with the environment to produce the final result evident in each patient. Based on novel insights provided by cardiac developmental biology, a common lineage ancestry of several HCM manifestations might be traced back to the pluripotent epicardium-derived cells, which early during heart development differentiate into interstitial fibroblasts, coronary smooth muscle cells, and atrio-ventricular endocardial cushions as mesenchymal cells. To date, the different faces of HCM have not been sufficiently liked or explained. We here attempt to address these issues by describing the various components of the disease, their origin, interaction, and clinical significance.

53. J Cardiovasc Transl Res. 2009 Dec;2(4):339-40. doi: 10.1007/s12265-009-9157-y.Epub 2009 Dec 4.

Hypertrophic cardiomyopathy at 50.

Yacoub M, Olivotto I, Cecchi F.

54. J Thorac Cardiovasc Surg. 2010 Nov;140(5):1046-52. doi: 10.1016/j.jtcvs.2010.02.020. Epub 2010 May 14.

Prevalence and clinical significance of acquired left coronary artery fistulas after surgical myectomy in patients with hypertrophic cardiomyopathy.

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OBJECTIVES: The relevance of iatrogenic left coronary artery fistulas complicating surgical myectomy in patients with hypertrophic cardiomyopathy is not known. We prospectively defined the echocardiographic features, prevalence, and clinical significance of left coronary artery fistulas in 40 consecutive patients with hypertrophic cardiomyopathy undergoing extended septal myectomy.
METHODS: Echocardiographic analysis was performed preoperatively and 1 and 6 months after surgical intervention. Diagnosis of left coronary artery fistulas required evidence of diastolic flow draining from the left ventricular wall into the left ventricular cavity according to prespecified criteria.
RESULTS: Left coronary artery fistulas were detected in 9 (23%) of the 40 study patients as a single occurrence in all except 1 patient, who had multiple fistulas. At 6 months, left coronary artery fistulas could still be detected in only 2 of the 9 patients. Of these, 1 patient remained asymptomatic but continued to show left coronary artery fistula persistence at 37 months postoperatively. The other, a woman with prior alcohol septal ablation, had progressive severe symptoms that required percutaneous closure of the fistula with a covered stent after angiographic identification of a large first septal branch fistula associated with distal left anterior descending coronary artery steal.
CONCLUSIONS: In patients with hypertrophic cardiomyopathy, left coronary artery fistulas are common in the early period after surgical myectomy, although their echocardiographic prevalence is dependent on operator awareness. Most left coronary artery fistulas heal spontaneously. Occasionally, however, fistulas can persist and cause symptoms requiring therapeutic intervention.

55. J Am Coll Cardiol. 2010 Apr 6;55(14):1444-53. doi: 10.1016/j.jacc.2009.11.062.

Clinical features and outcome of hypertrophic cardiomyopathy associated with triple sarcomere protein gene mutations.

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Comment in J Am Coll Cardiol. 2010 Apr 6;55(14):1454-5.

OBJECTIVES: The aim of this study was to describe the clinical profile associated with triple sarcomere gene mutations in a large hypertrophic cardiomyopathy (HCM) cohort.
BACKGROUND: In patients with HCM, double or compound sarcomere gene mutation heterozygosity might be associated with earlier disease onset and more severe outcome. The occurrence of triple mutations has not been reported.
METHODS: A total of 488 unrelated index HCM patients underwent screening for myofilament gene mutations by direct deoxyribonucleic acid sequencing of 8 genes, including myosin binding protein C (MYBPC3), beta-myosin heavy chain (MYH7), regulatory and essential light chains (MYL2, MYL3), troponin-T (TNNT2), troponin-I (TNNI3), alpha-tropomyosin (TPM1), and actin (ACTC).

RESULTS: Of the 488 index patients, 4 (0.8%) harbored triple mutations, as follows: MYH7-R869H, MYBPC3-E258K, and TNNI3-A86fs in a 32-year-old woman; MYH7-R723C, MYH7-E1455X, and MYBPC3-E165D in a 46-year old man; MYH7-R869H, MYBPC3-K1065fs, and MYBPC3-P371R in a 45-year old woman; and MYH7-R1079Q, MYBPC3-Q969X, and MYBPC3-R668H in a 50-year old woman. One had a history of resuscitated cardiac arrest, and 3 had significant risk factors for sudden cardiac death, prompting the insertion of an implantable cardioverter-defibrillator in all, with appropriate shocks in 2 patients. Moreover, 3 of 4 patients had a severe phenotype with progression to end-stage HCM by the fourth decade, requiring cardiac transplantation (n=1) or biventricular pacing (n=2). The fourth patient, however, had clinically mild disease.
CONCLUSIONS: Hypertrophic cardiomyopathy caused by triple sarcomere gene mutations was rare but conferred a remarkably increased risk of end-stage progression and ventricular arrhythmias, supporting an association between multiple sarcomere defects and adverse outcome. Comprehensive genetic testing might provide important insights to risk stratification and potentially indicate the need for differential surveillance strategies based on genotype.

56. Cardiovasc Ultrasound. 2010 Mar 17;8:7. doi: 10.1186/1476-7120-8-7.

Echocardiography in patients with hypertrophic cardiomyopathy: usefulness of old and new techniques in the diagnosis and pathophysiological assessment.

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Hypertrophic cardiomyopathy (HCM) is one of the most common inherited cardiomyopathy. The identification of patients with HCM is sometimes still a challenge. Moreover, the pathophysiology of the disease is complex because of left ventricular hyper-contractile state, diastolic dysfunction, ischemia and obstruction which can be coexistent in the same patient. In this review, we discuss the current and emerging echocardiographic methodology that can help physicians in the correct diagnostic and pathophysiological assessment of patients with HCM.

57. Zhonghua Xin Xue Guan Bing Za Zhi. 2009 Dec;37(12):1069-73.

[Myocardial hypoperfusion due to microvascular dysfunction in hypertrophic cardiomyopathy: role of positron emission tomography].

[Article in Chinese]

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Hypertrophic cardiomyopathy (HCM) is characterized by extreme clinical heterogeneity, ranging from sudden cardiac death to long-term disease progression and heart failure-related complications. Myocardial ischemia, occurring at the microvascular level, is a major determinant of clinical expression and outcome. Accordingly, the severity of this microvascular dysfunction has been shown to represent an early and powerful predictor of unfavorable outcome in HCM. The assessment of microvascular function in vivo is technically challenging, although critical to a truly comprehensive evaluation and risk stratification of HCM patients. Available technologies include positron emission tomography and cardiac magnetic resonance (CMR). Studies of regional myocardial blood flow using positron emission tomography have demonstrated that the vasodilator

response to dipyridamole is impaired in most HCM patients, not only in the hypertrophied ventricular septum but also in the less hypertrophied or non-thickened left ventricular free wall. CMR also allows measurement of myocardial flow, although the technique is currently time-consuming and largely limited to research situations. CMR provides further insight into the effects of ischemia in HCM patients, by visualizing the distribution and extent of fibrosis at the intramyocardial level. Late gadolinium enhancement (LGE) is a potential predictor of risk in HCM patients, and is believed to largely reflect replacement fibrosis resulting from recurrent microvascular ischemia. LGE is associated with increased prevalence of ventricular arrhythmias, and associated with microvascular dysfunction. The present review is to provide a concise overview for the available evidence of microvascular ischemia and its consequences in HCM.

58. Europace. 2010 Mar;12(3):347-55. doi: 10.1093/europace/euq013.

Efficacy of catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: impact of age, atrial remodelling, and disease progression.

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AIMS: In patients with hypertrophic cardiomyopathy (HCM) and atrial fibrillation (AF), radiofrequency catheter ablation (RFCA) represents a promising option. However, the predictors of RFCA efficacy remain largely unknown. We assessed the outcome of a multicentre HCM cohort following RFCA for symptomatic AF refractory to medical therapy.

METHODS AND RESULTS: Sixty-one patients (age 54 +/- 13 years; time from AF onset 5.7 +/- 5.5 years) with paroxysmal (n = 35; 57%), recent persistent (n = 15; 25%), or long-standing persistent AF (n = 11; 18%) were enrolled. A scheme with pulmonary vein isolation plus linear lesions was employed. Of the 61 patients, 32 (52%) required redo procedures. Antiarrhythmic therapy was maintained in 22 (54%). At the end of a 29 +/- 16 months follow-up, 41 patients (67%) were in sinus rhythm, including 17 of the 19 patients aged < or = 50 years, with marked improvement in New York Heart Association (NYHA) functional class (1.2 +/- 0.5 vs. 1.9 +/- 0.7 at baseline; P < 0.001). In the remaining 20 patients (33%), with AF recurrence, there was less marked, but still significant, improvement following RFCA (NYHA class 1.8 +/- 0.7 vs. 2.3 +/- 0.7 at baseline; P = 0.002).

Independent predictors of AF recurrence were increased left atrium volume [hazard ratio (HR) per unit increase 1.009, 95% confidence interval (CI) 1.001-1.018; P = 0.037] and NYHA functional class (HR 2.24, 95% CI 1.16-4.35; P = 0.016). Among 11 genotyped HCM patients (6 with MYBPC3, 2 with MYH7, 1 with MYL2 and 2 with multiple mutations), RFCA success rate was comparable with that of the overall cohort (n = 8; 73%).

CONCLUSION: RFCA was successful in restoring long-term sinus rhythm and improvingsymptomatic status in most HCM patients with refractory AF, including the subset with proven sarcomere gene mutations, although redo procedures were often necessary. Younger HCM patients with small atrial size and mild symptoms proved to be the best RFCA candidates, likely due to lesser degrees of atrial remodelling.

59. Zhonghua Xin Xue Guan Bing Za Zhi. 2009 Apr;37(4):303-7.

[Atrial fibrillation in hypertrophic cardiomyopathy: determinants, clinical course and management].

[Article in Chinese]

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Atrial fibrillation (AF) is the most common sustained arrhythmia in patients with hypertrophic cardiomyopathy (HCM), and represents an important complication in the clinical course of the disease, with adverse consequences on functional status and outcome. Studies on community-based HCM patient populations have shown that AF is associated with long-term clinical deterioration, cardioembolic stroke and increased cardiovascular mortality due to heart failure and stroke. Moreover, acute onset of AF may cause severe hemodynamic impairment and represent a trigger of potentially lethal ventricular arrhythmias. However, the consequences of AF on the long-term prognosis of HCM patients are not uniformly unfavorable, and may be compatible with an uneventful course, when properly managed. Management of AF in HCM is challenging, particularly when onset occurs at a young age. Both paroxysmal and permanent AF represent clear indications for oral anticoagulation. In most patients, maintenance of sinus rhythm is highly desirable but made difficult by the limited long-term efficacy and potentially hazardous side effects of available pharmacological options. In selected patients with HCM and severely symptomatic AF, radiofrequency catheter ablation may represent an effective therapeutic alternative, improving functional status, and reducing or postponing the need for antiarrhythmic drugs. In patients with persistent AF, in whom maintenance of sinus rhythm is not feasible, adequate ventricular rate control should be pursued aggressively by atrio-ventricular node blocking agents.

60. J Am Coll Cardiol. 2009 Aug 25;54(9):866-75. doi: 10.1016/j.jacc.2009.04.072.

The case for myocardial ischemia in hypertrophic cardiomyopathy.

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Since its original description 50 years ago, myocardial ischemia has been arecognized but underappreciated aspect of the pathophysiology of hypertrophic cardiomyopathy (HCM). Nevertheless, the assessment of myocardial ischemia is still not part of routine clinical diagnostic or management strategies. Morphologic abnormalities of the intramural coronary arterioles represent the primary morphologic substrate for microvascular dysfunction and its functional consequence-that is, blunted myocardial blood flow (MBF) during stress. Recently, a number of studies using contemporary cardiovascular imaging modalities such as positron emission tomography (PET) and cardiovascular magnetic resonance (CMR) have led to an enhanced understanding of the role that myocardial ischemia and its sequelae fibrosis play on clinical outcome. In this regard, studies with PET have shown that HCM patients have im paired MBF after dipyridamole infusion and that this blunted MBF is a powerful independent predictor of cardiovascular mortality and adverse LV remodeling associated with LV systolic dysfunction. Stress CMR with late gadolinium enhancement (LGE) has also shown that MBF is reduced in relation to magnitude of wall thickness and in those LV segments occupied by LGE (i.e., fibrosis). These CMR observations show an association between ischemia, myocardial fibrosis, and LV remodeling, providing support that abnormal MBF caused by microvascular dysfunction is responsible for myocardial ischemia-mediated myocyte death, and ultimately replacement fibrosis. Efforts should now focus on detecting myocardial ischemia before adverse LV remodeling begins, so that interventional treatment strategies can be initiated earlier in the clinical course to mitigate ischemia and beneficially alter the natural history of HCM.

61. J Electrocardiol. 2009 Nov-Dec;42(6):636-41. doi: 10.1016/j.jelectrocard.2009.06.002. Epub 2009 Jul 3.

Diagnostic accuracy of extended-length electrocardiogram in differentiating between athlete's heart and hypertrophic cardiomyopathy.

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BACKGROUND: Standard 12-lead electrocardiogram (ECG) has several limitations insolving the differential diagnosis between physiologic left ventricularhypertrophy (PLVH) and hypertrophic cardiomyopathy (HCM), given the high rate of false-positive results in athletes. The aim of this study was to assess the usefulness of several arrhythmic risk indexes in differentiating PLVH from HCM.
METHODS: A multiparametric ECG analysis (extended-length ECG) was performed on 30 male athletes with PLVH and 30 male patients with HCM, with homogeneous age distribution.
RESULTS: The combination of 4 extended-length ECG variables, namely, corrected QT interval (Bazett), QT dispersion, mean resting heart rate, and low-amplitude signal duration at 25 Hz (low-amplitude signal duration at the end of filtered QRS) displayed remarkable diagnostic accuracy (area under receiver operating characteristic curve, 94%). The same accuracy was obtained replacing QT dispersion with T-wave complexity index.
CONCLUSIONS: Extended-length ECG can be considered an effective, low-cost, and low time-consuming clinical tool for distinguishing between PLVH and HCM.

62. Eur Heart J. 2009 Jul;30(13):1549-50. doi: 10.1093/eurheartj/ehp216. Epub 2009 Jun 1.

Myocardial bridging and sudden death in hypertrophic cardiomyopathy: Salome drops another veil.

Olivotto I, Cecchi F, Yacoub MH.

Comment on Eur Heart J. 2009 Jul;30(13):1627-34.

63. Nat Rev Cardiol. 2009 Apr;6(4):317-21. doi: 10.1038/nrcardio.2009.9.

Developmental origins of hypertrophic cardiomyopathy phenotypes: a unifying hypothesis.

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The majority of genetic mutations associated with hypertrophic cardiomyopathy (HCM) occur in genes encoding sarcomeric proteins, which are expressed only in cardiomyocytes. However, some manifestations of the HCM phenotype, such as myocardial disarray, interstitial fibrosis, mitral valve abnormalities, andmicrovascular remodeling, indicate the involvement of other cell lineages. The link between sarcomeric gene defects and these 'extended' HCM phenotypes remains elusive. Based on novel insights provided by cardiac developmental biology, we propose that a common lineage ancestry of the diverse HCM phenotypes not involving the cardiomyocyte can be traced to the pluripotent epicardium-derived cells (EPDCs). During cardiac colonization, EPDCs differentiate into interstitial fibroblasts, coronary smooth-muscle cells, and atrioventricular endocardial cushions

as mesenchymal cells. We propose that the cross-talk between healthy EPDCs and abnormally contracting cardiomyocytes might account for the diverse manifestations of HCM, by a putative mechanism of mechanotransduction leading to abnormal gene expression and differentiation.

64. J Nucl Cardiol. 2009 Jan-Feb;16(1):92-6. doi: 10.1007/s12350-008-9005-5. Epub 2009 Jan 20.

Relationship between atrial fibrillation and blunted hyperemic myocardial blood flow in patients with hypertrophic cardiomyopathy.

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BACKGROUND: Atrial fibrillation (AF) and coronary microvascular dysfunction (CMD) are common in hypertrophic cardiomyopathy (HCM), but whether they are associated is unclear. We assessed the relationship between AF and CMD in HCM.
METHODS AND RESULTS: Global hyperemic myocardial blood flow (hMBF) was measured in 95 HCM patients (16 with, 79 without paroxysmal or chronic AF) by N-13 ammonia positron emission tomography (PET) after dipyridamole infusion. AF patients were older (50.5 +/- 13.4 vs. 38.7 +/- 14.9 years, P < .0005), had larger left atrial diameter (49.8 +/- 7.4 vs 38.6 +/- 5.7 mm, P < .00001), and left ventricular end-systolic diameter (30.4 +/- 6.7 vs 25.5 +/- 5.3 mm, P < .005) compared with those in stable sinus rhythm. In patients with AF, hMBF was significantly lower (1.23 +/- 0.44 vs 1.87 +/- 0.90 mL/min/g, P < 0.0001). In multivariate logistic regression analysis, hMBF, left atrial diameter, and age were independently associated with AF (P < .05 for all).
CONCLUSIONS: HCM patients with paroxysmal or chronic AF have lower hMBF than those in stable sinus rhythm. The association between CMD and AF is independent of other known predictors of AF, suggesting a causal link between these two features.

65. Nat Clin Pract Cardiovasc Med. 2009 Feb;6(2):134-9. doi: 10.1038/ncpcardio1420.Epub 2008 Dec 17.

Tunneled left anterior descending artery in a child with hypertrophic cardiomyopathy.

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BACKGROUND: A 10-year-old boy presented with a history of severe angina on exertion. A two-dimensional echocardiogram showed mild asymmetric left ventricular (LV) hypertrophy localized to the interventricular septum, consistent with nonobstructive hypertrophic cardiomyopathy. A maximal treadmill exercise test was terminated early owing to marked downsloping of the ST-T segment on all precordial leads, associated with mild chest discomfort. Cardiac MRI and coronary angiography showed that the left anterior descending (LAD) artery was 'tunneled' from its origin to the junction of the middle and lower segments, causing systolic obliteration. PET showed diffusely blunted myocardial blood flow after dipyridamole infusion. A beating-heart technique was used to perform surgical mobilization of the superficial and lateral surfaces of the LAD artery. The patient was free from angina at 6 months after surgery. A repeat exercise test showed considerable improvement in exercise tolerance, which was associated with a marked decrease in ST-T changes on exertion.

INVESTIGATIONS: Physical examination, laboratory tests, 12-lead electrocardiography, two-dimensional echocardiography, exercise testing, cardiac MRI, coronary angiography, PET, Holter electrocardiographic monitoring.
DIAGNOSIS: Angina caused by extensive myocardial tunneling of the LAD artery in nonobstructive hypertrophic cardiomyopathy.
MANAGEMENT: Bisoprolol therapy and surgical mobilization of the tunneled LAD artery.

66. J Am Coll Cardiol. 2008 Aug 12;52(7):559-66. doi: 10.1016/j.jacc.2008.04.047.

Assessment and significance of left ventricular mass by cardiovascular magnetic resonance in hypertrophic cardiomyopathy.

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Comment in J Am Coll Cardiol. 2009 Jan 27;53(4):399; author reply 399, J Am Coll Cardiol. 2008 Aug 12;52(7):567-8.

OBJECTIVES: Our aim was to assess the distribution and clinical significance of left ventricular (LV) mass in patients with hypertrophic cardiomyopathy (HCM).
BACKGROUND: Hypertrophic cardiomyopathy is defined echocardiographically by unexplained left ventricular wall thickening. Left ventricular mass, quantifiable by modern cardiovascular magnetic resonance techniques, has not been systematically assessed in this disease.
METHODS: In 264 HCM patients (age 43 +/- 18 years; 75% men), LV mass by cardiovascular magnetic resonance was measured, indexed by body surface area, and compared with that in 606 healthy control subjects.
RESULTS: The LV mass index in HCM patients significantly exceeded that of control subjects (104 +/- 40 g/m(2) vs. 61 +/- 10 g/m(2) in men and 89 +/- 33 g/m(2) vs. 47 +/- 7 g/m(2) in women; both $p < 0.0001$). However, values were within the normal range (< or = mean +2 SDs for control subjects) in 56 patients (21%), and only mildly increased (mean +2 to 3 SDs) in 18 (16%). The LV mass index showed a modest relationship to maximal LV thickness ($r(2) = 0.38$; $p < 0.001$), and was greater in men (104 +/- 40 g/m(2) vs. 89 +/- 33 g/m(2) in women; $p < 0.001$) and in patients with resting outflow obstruction (121 +/- 43 g/m(2) vs. 96 +/- 37 g/m(2) in nonobstructives; $p < 0.001$). During a 2.6 +/- 0.7-year follow-up, markedly increased LV mass index proved more sensitive in predicting outcome (100%, with 39% specificity), whereas maximal wall thickness >30 mm was more specific (90%, with 41% sensitivity).
CONCLUSIONS: In distinction to prior perceptions, LV mass index was normal in about 20% of patients with definite HCM phenotype. Therefore, increased LV mass is not a requirement for establishing the clinical diagnosis of HCM. The LV mass correlated weakly with maximal wall thickness, and proved more sensitive in predicting outcome.

67. J Physiol. 2008 Aug 1;586(15):3639-44. doi: 10.1113/jphysiol.2008.155952. Epub 2008 Jun 19.

The familial hypertrophic cardiomyopathy-associated myosin mutation R403Q accelerates tension generation and relaxation of human cardiac myofibrils.

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The R403Q mutation in beta-myosin heavy chain was the first mutation to be identified as responsible for familial hypertrophic cardiomyopathy (FHC). In spite of extensive work on the functional sequelae of this mutation, the mechanism by which the mutant protein causes the disease has not been definitely identified. Here we directly compare contraction and relaxation mechanics of single myofibrils from left ventricular samples of one patient carrying the R403Q mutation to those from a healthy control heart. Tension generation and relaxation following sudden increase and decrease in [Ca(2+)] were much faster in the R403Q myofibrils with relaxation rates being the most affected parameters. The results show that the R403Q mutation leads to an apparent gain of protein function but a greater energetic cost of tension generation. Increased energy cost of tension generation may be central to the FHC disease process, help explain some unresolved clinical observations, and carry significant therapeutic implications.

68. J Nucl Med. 2008 Jul;49(7):1090-6. doi: 10.2967/jnumed.107.050138. Epub 2008 Jun 13.

Spatial relationship between coronary microvascular dysfunction and delayed contrast enhancement in patients with hypertrophic cardiomyopathy.

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To clarify the spatial relationship between coronary microvascular dysfunction and myocardial fibrosis in hypertrophic cardiomyopathy (HCM), we compared the measurement of hyperemic myocardial blood flow (hMBF) by PET with the extent of delayed contrast enhancement (DCE) detected by MRI.
METHODS: In 34 patients with HCM, PET was performed using (13)N-labeled ammonia during hyperemia induced by intravenous dipyridamole. DCE and systolic thickening were assessed by MRI. Left ventricular myocardial segments were classified as with DCE, either transmural (DCE-T) or nontransmural (DCE-NT), and without DCE, either contiguous to DCE segments (NoDCE-C) or remote from them (NoDCE-R).
RESULTS: In the group with DCE, hMBF was significantly lower than in the group without DCE (1.81 +/- 0.94 vs. 2.13 +/- 1.11 mL/min/g; $P < 0.001$). DCE-T segments had lower hMBF than did DCE-NT segments (1.43 +/- 0.52 vs. 1.91 +/- 1 mL/min/g, $P < 0.001$). Similarly, NoDCE-C segments had lower hMBF than did NoDCE-R (1.98 +/- 1.10 vs. 2.29 +/- 1.10 mL/min/g, $P < 0.01$) and had no significant difference from DCE-NT segments. Severe coronary microvascular dysfunction (hMBF in the lowest tertile of all segments) was more prevalent among NoDCE-C than NoDCE-R segments (33% vs. 24%, $P < 0.05$). Systolic thickening was inversely correlated with percentage transmurality of DCE (Spearman rho = -0.37, $P < 0.0001$) and directly correlated with hMBF (Spearman rho = 0.20, $P < 0.0001$).
CONCLUSION: In myocardial segments exhibiting DCE, hMBF is reduced. DCE extent is inversely correlated and hMBF directly correlated with systolic thickening. In segments without DCE but contiguous to DCE areas, hMBF is significantly lower than in those remote from DCE and is similar to the value obtained in nontransmural DCE segments. These results suggest that increasing degrees of coronary microvascular dysfunction might play a causative role for myocardial fibrosis in HCM.

69. Mayo Clin Proc. 2008 Jun;83(6):630-8. doi: 10.4065/83.6.630.

Myofilament protein gene mutation screening and outcome of patients with

hypertrophic cardiomyopathy.

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Comment in Mayo Clin Proc. 2008 Jun;83(6):626-7.

OBJECTIVE: To determine the influence of a positive genetic test for hypertrophic cardiomyopathy (HCM) on clinical outcome.
PATIENTS AND METHODS: A cohort of 203 unrelated patients with HCM (mean +/- SD age, 50+/-18 years) was enrolled from January 1, 2002, through December 31, 2003. They were followed up for a mean +/- SD time of 4.0+/-1.7 years after genetic testing of the 8 HCM-susceptibility genes that encode key sarcomeric/myofilament proteins. The clinical phenotype of those with a positive genetic test (myofilament-positive HCM) was compared with those with a negative genetic test (myofilament-negative HCM).
RESULTS: In this cohort of 203 patients, 87 mutations were identified in 126 patients (myofilament-positive HCM, 62%); the remaining 77 patients (38%) were myofilament-negative. Despite similar baseline features, patients with myofilament-positive HCM showed increased risk of the combined end points of cardiovascular death, nonfatal stroke, or progression to New York Heart Association class III or IV compared with the patients with myofilament-negative HCM (25% vs 7%, respectively; independent hazard ratio, 4.27; P=.008). These end points occurred at any age among patients with myofilament-positive HCM (range, 14-86 years), but only in those aged 65 years and older among patients with myofilament-negative HCM. Moreover, patients with myofilament-positive HCM showed greater probability of severe left ventricular systolic and diastolic dysfunction, defined as an ejection fraction of less than 50% and a restrictive filling pattern (P=.02 and P<.02, respectively, vs myofilament-negative HCM).
CONCLUSION: Screening for sarcomere protein gene mutations in HCM identifies a broad subgroup of patients with increased propensity toward long-term impairment of left ventricular function and adverse outcome, irrespective of the myofilament (thick, intermediate, or thin) involved.

70. Eur Heart J. 2008 Jan;29(2):270-6. Epub 2007 Oct 4.

Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases.

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Comment in Eur Heart J. 2008 Jan;29(2):144-6, Eur Heart J. 2008 Apr;29(8):1073-4; author reply 1074.

In biology, classification systems are used to promote understanding and systematic discussion through the use of logical groups and hierarchies. In clinical medicine, similar principles are used to

standardise the nomenclature of disease. For more than three decades, heart muscle diseases have been classified into primary or idiopathic myocardial diseases (cardiomyopathies) and secondary disorders that have similar morphological appearances, but which are caused by an identifiable pathology such as coronary artery disease or myocardial infiltration (specific heart muscle diseases). In this document, The European Society of Cardiology Working Group on Myocardial and Pericardial Diseases presents an update of the existing classification scheme. The aim is to help clinicians look beyond generic diagnostic labels in order to reach more specific diagnoses.

71. J Am Coll Cardiol. 2007 Aug 28;50(9):831-4. Epub 2007 Aug 13.

Surgical myectomy versus alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Will there ever be a randomized trial?

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Comment in J Am Coll Cardiol. 2008 Mar 25;51(12):1233-4; author reply 1234-5.

Dynamic left ventricular outflow tract obstruction is an important pathophysiologic feature of hypertrophic cardiomyopathy (HCM) and a predictor of clinical deterioration and cardiovascular mortality. Patients with marked obstruction and severe limiting symptoms refractory to maximum medical management are considered candidates for invasive septal reduction therapy, which includes surgical myectomy and alcohol septal ablation (ASA). Availability of both surgical myectomy and ASA has polarized the cardiovascular community concerning the most appropriate implementation of these two interventions. The ensuing controversy of whether myectomy and ASA are truly equivalent options has resulted in calls for a prospective randomized trial. However, upon analysis, such a myectomy versus ASA trial, adequately powered to compare the key issue of long-term outcome, poses a myriad of practical problems that seem virtually insurmountable. Therefore, it is appropriate to revisit this evolving debate at this time, identify the unique obstacles to a randomized study design, and achieve some clarity concerning the most realistic clinical strategies for symptomatic patients with HCM and outflow obstruction.

72. Am J Cardiol. 2007 Jun 1;99(11):1575-81. Epub 2007 Apr 24.

Usefulness and safety of transcatheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy.

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Atrial fibrillation (AF) is common in patients with hypertrophic cardiomyopathy (HC) and predicts adverse outcome. Radiofrequency catheter ablation (RFCA) represents a potentially advantageous alternative to lifelong pharmacologic treatment. However, its efficacy in patients with HC is not established. In the present study, the feasibility, safety, and efficacy of RFCA of AF in patients with HC were evaluated. Twenty-six patients with HC with paroxysmal (n = 13) or permanent (n = 13) AF refractory to antiarrhythmic therapy (age 58 +/- 11 years, time from AF onset 7.3 +/- 6.2 years, left atrial volume 170 +/- 48 ml) underwent RFCA. A schema with pulmonary vein isolation plus linear

lesions was used. No major periprocedural complication occurred. One patient died from a hemorrhagic stroke 4 weeks after RFCA while in sinus rhythm. During a 19 +/- 10-month follow-up, 9 of the remaining 25 patients (36%) experienced recurrence of AF (despite repeated RFCA in 3) and were considered failures, whereas 16 remained in sinus rhythm (i.e., 64% overall success rate). Ten of these 16 patients were off antiarrhythmic drug therapy at final evaluation. RFCA was highly successful in patients with paroxysmal AF (77% success rate compared with 50% in the subgroup with permanent AF). Patients with restoration of sinus rhythm showed marked symptomatic improvement (final New York Heart Association functional class 1.2
+/- 0.5 vs 1.7 +/- 0.7 before the procedure, p = 0.003). Conversely, patients for whom RFCA failed showed no change (final functional class 1.9 +/- 0.8 vs 1.7 +/- 0.9 before the procedure, p = 0.59). In conclusion, in most studied patients with HC, RFCA proved a safe and effective therapeutic option for AF, improved functional status, and was able to reduce or postpone the need for long-term pharmacologic treatment.

73. Nat Clin Pract Cardiovasc Med. 2007 May;4(5):232-3.

'End-stage' hypertrophic cardiomyopathy: from mystery to model.

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74. Eur Heart J. 2007 May;28(9):1170. Epub 2007 Mar 28.

ECG-based screening: not only for athletes.

Nistri S, Olivotto I, Cecchi F, Basso C, Thiene G.

Comment on Eur Heart J. 2006 Sep;27(18):2196-200.

75. Nat Clin Pract Cardiovasc Med. 2007 Apr;4(4):194-5. Epub 2007 Feb 27.

Does LV outflow tract obstruction increase the risk of sudden death in hypertrophic cardiomyopathy?

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Comment on Eur Heart J. 2006 Aug;27(16):1933-41.

76. Herz. 2006 Dec;31(9):871-6.

Midventricular obstruction and clinical decision-making in obstructive hypertrophic cardiomyopathy.

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The presence of intraventricular obstruction is a powerful predictor of outcome in patients with hypertrophic cardiomyopathy (HCM) and, when associated with severe, drug-refractory symptoms, should be managed aggressively. Resting left ventricular outflow obstruction is found in approximately 20% of the patients, classically occurs at the subaortic level, and is associated with mitral valve systolic anterior motion (SAM). In a minority of patients, however, the impedance

to flow occurs at midventricular level, unrelated to SAM. Symptomatic midventricular obstruction represents a clinical challenge, and its treatment is not standardized. In these patients, both surgical myectomy and alcohol septal ablation (ASA) are technically feasible. A rational approach to the management of these patients depends on accurate characterization of the pathophysiology, coupled with comparison of the results of different management strategies. To illustrate these points, the details of a patient who first underwent percutaneous ASA and subsequently required redo surgical treatment are described here, with special emphasis on the implications to the management of midventricular obstruction, as well as to the more global issue of obstructive HCM.

77. Am J Cardiol. 2006 Oct 1;98(7):960-5. Epub 2006 Aug 14.

Prognostic significance of left atrial size in patients with hypertrophic cardiomyopathy (from the Italian Registry for Hypertrophic Cardiomyopathy).

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Comment in Am J Cardiol. 2007 Mar 15;99(6):877-8.

This study assessed left atrial (LA) dimension as a potential predictor of outcome in hypertrophic cardiomyopathy (HC). From the Italian Registry for Hypertrophic Cardiomyopathy, 1,491 patients (mean age 47 +/- 17 years; 61% men; 19% obstructive), followed for 9.4 +/- 7.4 years after the initial echocardiographic evaluation, constituted the study group. The mean LA transverse dimension was 43 +/- 9 mm and was larger in patients with severe symptoms (48 +/- 9 mm for New York Heart Association classes III and IV vs 42 +/- 9 mm for classes I and II, p <0.001), atrial fibrillation (47 +/- 9 vs 42 +/- 8 mm in sinus rhythm, p <0.001), and left ventricular outflow obstruction (46 +/- 9 mm for >or=30 mm Hg at rest vs 42 +/- 9 mm for <30 mm Hg at rest, p <0.001). On univariate analysis, each 5-mm increase in LA size was associated with a hazard ratio (HR) of 1.2 for all-cause mortality (p <0.0001). On multivariate analysis, a LA dimension >48 mm (the 75th percentile) had a HR of 1.9 for all-cause mortality (p = 0.008), 2.0 for cardiovascular death (p = 0.014), and 3.1 for death related to heart failure (p = 0.008) but was unassociated with sudden death (p = 0.81). Similar results were obtained after the exclusion of patients with atrial fibrillation (HR 1.7, p = 0.008) or outflow obstruction (HR 1.8, p = 0.003). The predictive power of LA dimension >48 mm was also validated in an independent HC cohort from the United States, with similar HRs (1.8 for all-cause mortality, p = 0.019). In conclusion, in a large cohort of patients with HC from a nationwide registry, a marked increase in LA dimension were predictive of long-term outcome, independent of co-existent atrial fibrillation or outflow obstruction. LA dimension is a novel and independent marker of prognosis in HC, particularly relevant to the identification of patients at risk for death related to heart failure.

78. J Cardiovasc Med (Hagerstown). 2006 Aug;7(8):601-7.

A molecular screening strategy based on beta-myosin heavy chain, cardiac myosin binding protein C and troponin T genes in Italian patients with hypertrophic cardiomyopathy.

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BACKGROUND: Mutations causing hypertrophic cardiomyopathy (HCM) have been described in nine different genes of the sarcomere. Three genes account for most known mutations: beta-myosin heavy chain (MYH7), cardiac myosin binding protein C (MYBPC3) and cardiac troponin T (TNNT2). Their prevalence in Italian HCM patients is unknown. Thus, we prospectively assessed a molecular screening strategy of these three genes in a consecutive population with HCM from two Italian centres.
METHODS: Comprehensive screening of MYBPC3, MYH7 and TNNT2 was performed in 88 unrelated HCM patients by denaturing high-performance liquid chromatography and automatic sequencing.
RESULTS: We identified 32 mutations in 50 patients (57%); 16 were novel. The prevalence rates for MYBPC3, MYH7 and TNNT2 were 32%, 17% and 2%, respectively. MYBPC3 mutations were 18, including two frameshift, five splice-site and two nonsense. All were 'private' except insC1065 and R502Q, present in three and two patients, respectively. Moreover, E258K was found in 14% of patients, suggesting a founder effect. MYH7 mutations were 12, all missense; seven were novel. In TNNT2, only two mutations were found. In addition, five patients had a complex genotype [i.e. carried a double MYBPC3 mutation (n = 2), or were double heterozygous for mutations in MYBPC3 and MYH7 (n = 3)].
CONCLUSIONS: The first comprehensive evaluation of MYBPC3, MYH7 and TNNT2 in an Italian HCM population allowed a genetic diagnosis in 57% of the patients. These data support a combined analysis of the three major sarcomeric genes as a rational and cost-effective initial approach to the molecular screening of HCM.

79. J Am Coll Cardiol. 2006 Mar 7;47(5):1043-8.

Relevance of coronary microvascular flow impairment to long-term remodeling and systolic dysfunction in hypertrophic cardiomyopathy.

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OBJECTIVES: This study sought to evaluate whether the entity of microvascular dysfunction, assessed by positron emission tomography (PET), predicts the long-term development of left ventricular (LV) remodeling and systolic dysfunction in hypertrophic cardiomyopathy (HCM).
BACKGROUND: A subgroup of patients with HCM developed LV dilation and systolic impairment. A causal role of coronary microvascular dysfunction has been suggested as the underlying pathophysiological mechanism.
METHODS: Fifty-one patients (New York Heart Association functional class I to II) were followed up for 8.1 +/- 2.1 years after measurement of resting and dipyridamole (Dip) myocardial blood flow (MBF). Left ventricular systolic dysfunction was defined as an ejection fraction (LVEF) <50%.
RESULTS: The Dip-MBF was blunted in HCM patients compared with a group of healthy control patients (1.50 +/- 0.69 ml/min/g vs. 2.71 +/- 0.94 ml/min/g; p < 0.001). At final evaluation, 11 patients (22%) had an LVEF <50%; in most (n = 7), systolic dysfunction was associated with a significant increase in LV cavity dimensions (>5 mm) during follow-up. These 11 patients showed lower Dip-MBF than the 40 with preserved LV function (1.04 +/- 0.38 ml/min/g vs. 1.63 +/- 0.71 ml/min/g, respectively; p = 0.001); Dip-MBF was particularly blunted in five patients with clinical progression to severe heart failure symptoms or death (Dip-MBF 0.89 +/- 0.15 ml/min/g). At multivariate analysis, the two independent predictors of systolic dysfunction were Dip-MBF in the lowest tertile (<1.1 ml/min/g; relative hazard, 7.5; p = 0.038) and an end-diastolic LV dimension in

the highest tertile (>45 mm; relative hazard, 12.3; p = 0.031).
CONCLUSIONS: Severe microvascular dysfunction is a potent long-term predictor of adverse LV remodeling and systolic dysfunction in HCM. Our findings indicate microvascular dysfunction as a potential target for prevention of disease progression and heart failure in HCM.

80. Am Heart J. 2005 Nov;150(5):947-54.

The Italian Registry for hypertrophic cardiomyopathy: a nationwide survey.

Cecchi F(1), Olivotto I, Betocchi S, Rapezzi C, Conte MR, Sinagra G, Zachara E, Gavazzi A, Rordorf R, Carnemolla G, Porcu M, Nistri S, Gruppillo P, Giampaoli S.
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BACKGROUND: National registries are advocated as instrumental to the solution of rarity-related problems for patients with hypertrophic cardiomyopathy (HCM), including limited access to advanced treatment options. Thus, an Italian Registry for HCM was created to assess the clinical profile and the level of care nationwide of patients with HCM.
METHODS: Cardiology centers over the national territory were recruited to provide clinical data of all patients with HCM ever seen at each institution. The enrollment period was from May 2000 to May 2002.
RESULTS: The registry enrolled 1677 patients from 40 institutions. Most (69%) were followed at referral centers, whereas 31% were from community centers with intermediate-low patient flow. Patients diagnosed after routine medical examinations or familial screenings were 39%. Most patients were male (62%), in their fourth to sixth decade of life, and in New York Heart Association class I to II (89%); 24% had resting left ventricular obstruction and 18% had atrial fibrillation. During a 9.7-year average follow-up, cardiovascular mortality was 1%/y, mostly because of heart failure, with no significant change over the last 3 decades; sudden death was less common (0.4%/y). Only 4% of patients received a defibrillator; 14% of the 401 patients with LV outflow obstruction underwent invasive relief of obstruction; and <1% were offered genetic analyses or counseling.
CONCLUSIONS: The Italian Registry represents the first comprehensive attempt to evaluate the clinical impact and management of HCM at a national level. Findings underscore the role of screening strategies for an early diagnosis and suggest limited use of the advanced therapeutic options for HCM.