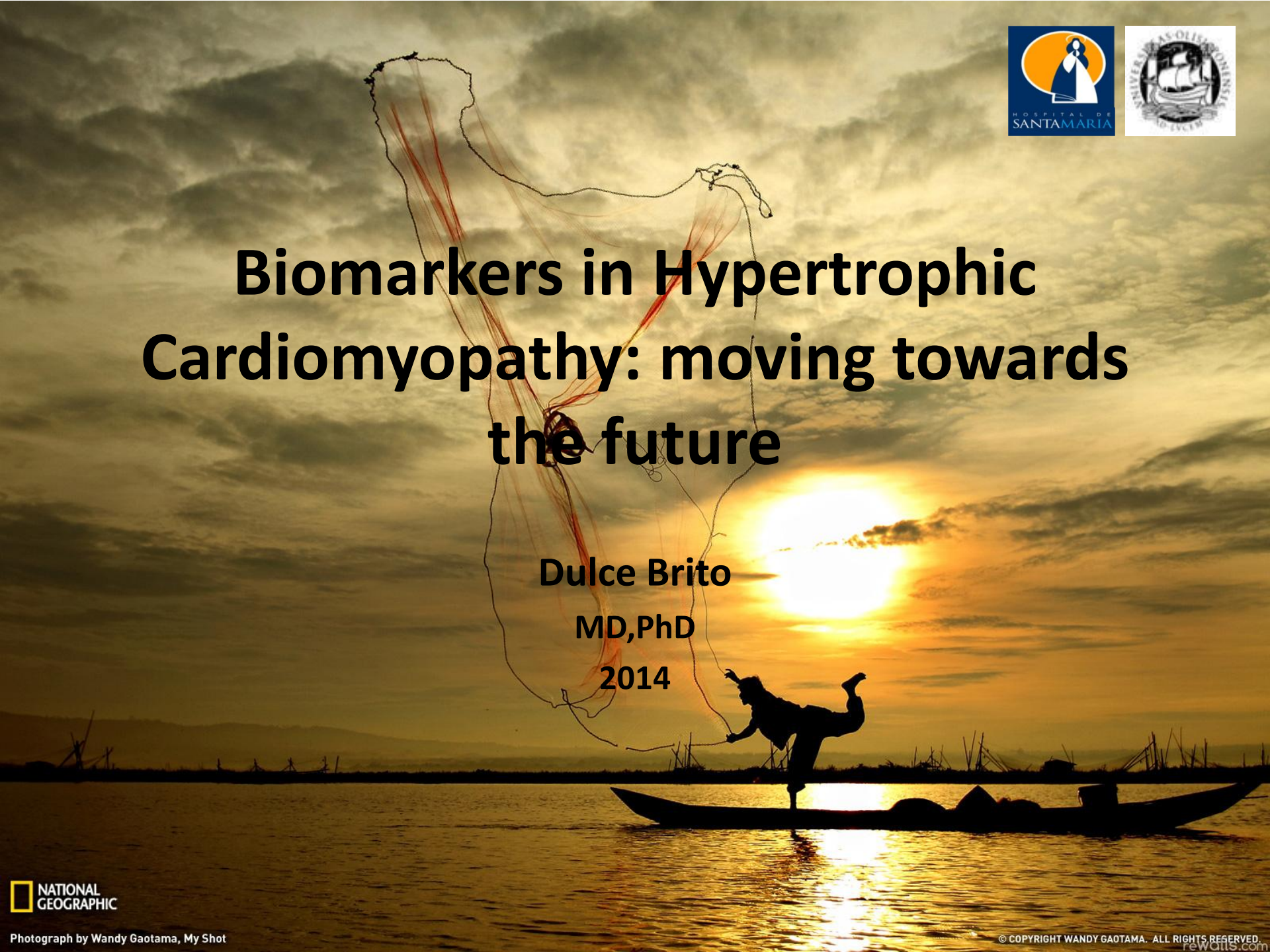


Biomarkers in Hypertrophic Cardiomyopathy: moving towards the future

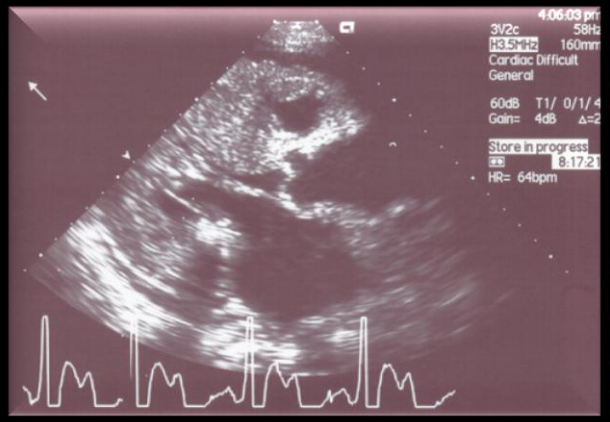
Dulce Brito

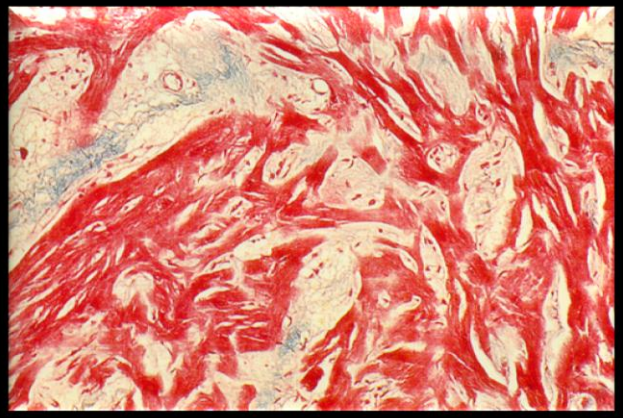
MD,PhD

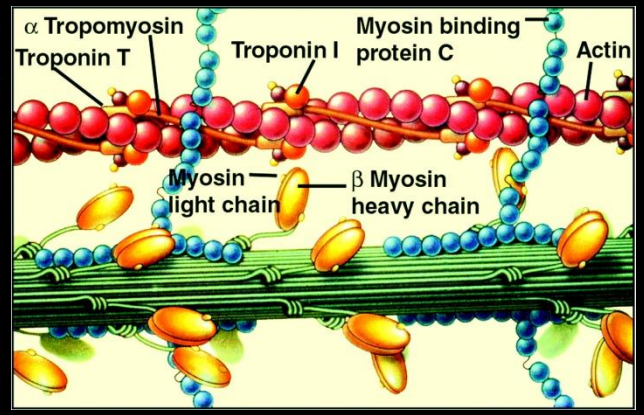
2014

Hypertrophic cardiomyopathy (HCM)

Prevalence: 1/500 – the most common genetic (monogenic) cardiovascular disease







Clinical diagnosis

Unexplained LVH

SCD risk: 2-6%/y
(*major clinical RF*) - ICD

Pathological diagnosis

"Disarray"
Small vessel disease
↓
LV dysfunction
Arrithmias
Ischemia
↓
SCD, CHF, CVA

Genetic diagnosis

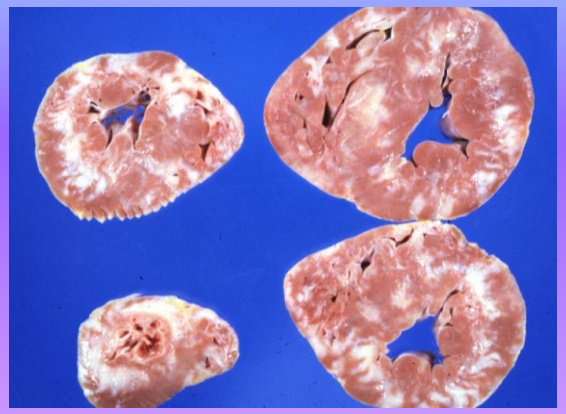
Sarcomere disease
Autoss. dominant

≈ 1000(?) mutations (>12 genes)
MYH7, MYBPC3 - > 80%
TNNT2, TNNI3

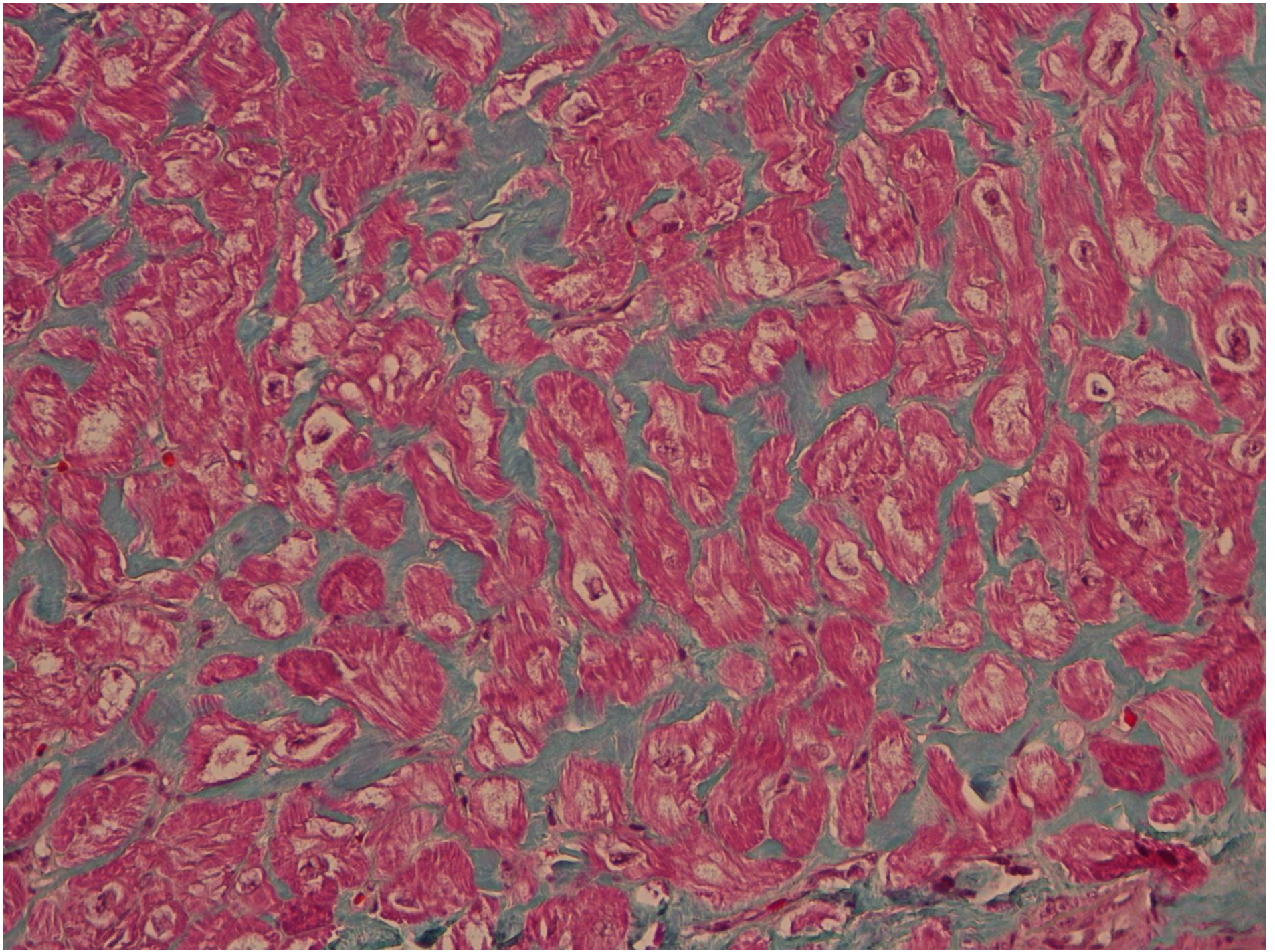
(identified mutations in 2/3)

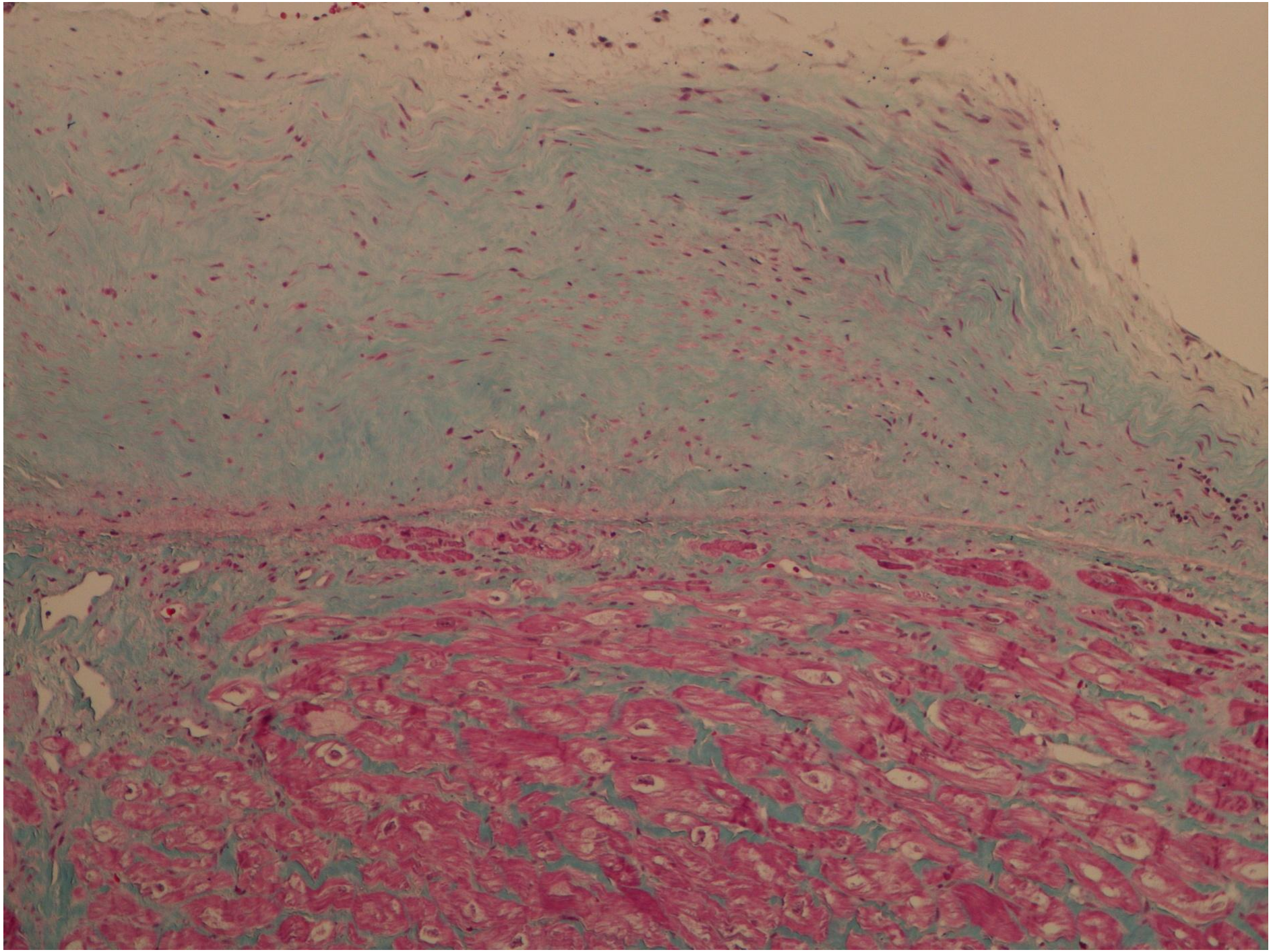
Biomarkers in HCM: moving towards the future

- **It is the most common cause of sudden death in young adults, otherwise healthy** *(Marian AJ. Lancet 2000).*
- **Diastolic dysfunction is universally present in overt disease and a significant cause of heart failure (HF)**
- **Cardiac fibrosis is a hallmark of HCM**
  - **… and is considered to be a substrate for ventricular arrhythmias, sudden cardiac death, left ventricular dysfunction, remodeling and HF** *(Shirani J et al. JACC 2000; Choudhury L et al. JACC 2002;Varnava AM et al. Heart 2000).*



  - **In the presence of LVH, fibrosis is universally detected in myocardial biopsy samples and biomarkers reflecting collagen metabolism suggest that collagen turnover is increased** *(Lombardi R et al. Circulation 2003; Fassbach M et al. Z Kardiol 2005; Ho CY et al. N Engl J Med 2010).*
  - **Fibrosis can also be visualized by gadolinium-enhanced cardiac magnetic resonance imaging (MRI)** (*Choudhury L et al. JACC 2002; Moon JC et al. JACC 2003; Maron MS et al. Circ Heart Fail 2008; Rudolph A et al JACC 2009)*





Biomarkers in HCM: moving towards the future

Any intervention in overt disease has been mainly for treating symptoms and for prevention of sudden death, on the basis of the well-known clinical risk factors recognized to date …

- **First-degree relatives of index patients have a 50% chance of inheriting the condition** *(Maron BJ et al. JACC 2003; Elliot P et al. Eur Heart J 2008)*

- **The early identification of HCM mutation carriers before they develop the phenotype (fibrosis and cardiac hypertrophy) is mandatory with the aim of an eventual early preventive intervention** *(Marian AJ. J Cardiovasc Transl Res 2009).*

- **Genetic testing is the ideal strategy for the identification of HCM mutation carriers but it requires the identification of the causal mutation in the index patient. Moreover, this process is expensive, not always available and fails to identify causal mutations in 30% to 40% of probands** *(Marian AJ et al. Circulation 2003; Brito D et al. Rev Port Cardiol 2012)*

Biomarkers in HCM: moving towards the future

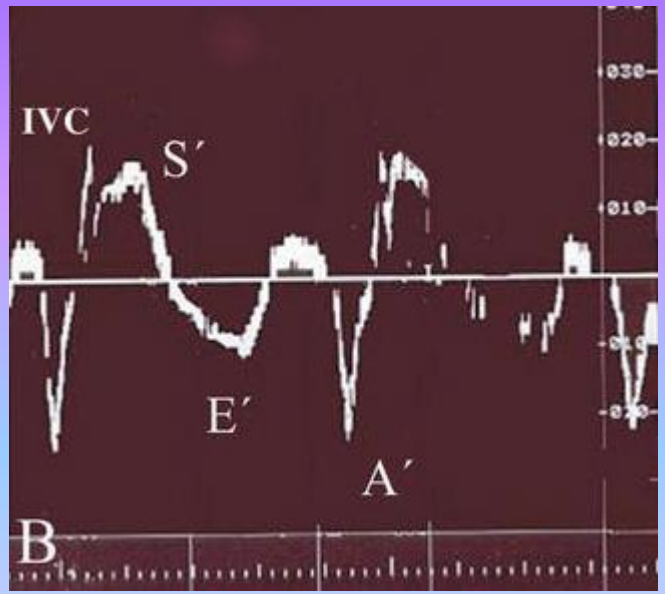
- **Animal studies indicate that a profibrotic milieu is present early in hearts with HCM** *(Geisterfer-Lowrance AA et al. Science 1996; Kim JB et al. Science 2007)*

- **The trigger for fibrosis is unknown but sarcomere mutation carriers show evidence of increased collagen synthesis before the development of LVH and in the absence of visible fibrosis on cardiac MRI**

  (Ho CY et al. N Engl J Med 2010)

- **Also left ventricular relaxation may be impaired in mutation carriers without LVH indicating that sarcomere mutations may have impact on diastolic function**

  (Nagueh SF et al. Circulation 2001; Ho CY et al. Circulation 2002; Cardim N. Am J Cardiol 2002)



Biomarkers in HCM: moving towards the future

- **The early identification of (echo) parameters, prior t attractive and attempted discrepant and do not see diagnosis of HCM** *(Nagueh SF e et al Eur Heart J 2010; De S. et al, Am H*

NT-proBNP Plasmático: Um Marcador Bioquímico de Hipertrofia Ventricular na Miocardiopatia Hipertrófica [102]

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Rev Port Cardiol 2004;23(12):1557-1582

Tissue Doppler Imaging and Plasma N-Terminal Probrain Natriuretic Peptide for the Identification of Hypertrophic Cardiomyopathy Mutation Carriers

Doroteia Silva, MD[a,*], Hugo Madeira, MD, PhD[b], Augusto Almeida, MSc[c], and Dulce Brito, MD, PhD[a,b]

Am J Cardiol 2013

Plasma NT-proBNP levels – a biomarker of myocardial stress – although usually high in overt disease and correlating with myocardial mass, were not useful for a preclinical diagnosis of carriers *(Brito D et al. Rev Port Cardiol 2004; Silva D et al. Am J Cardiol 2013).*

Biomarkers in HCM: moving towards the future

- **Galectin-3 (Gal-3), a beta-galactoside-binding lectin, is a mediator of cardiac fibrosis.**
- **Gal-3 is expressed in activated macrophages and it induces fibroblast proliferation, collagen deposition and ventricular dysfunction.**
- **In clinical studies, Gal-3 is correlated with markers of extracellular matrix turnover, supporting its role in collagen metabolism. Evidence suggests that Gal-3 may play a causal role in cardiac remodeling.**
- **Higher circulating Gal-3 concentrations have been related to mortality in patients with acute and chronic heart failure as well as in the general population and seem to be associated with risk for new-onset HF in apparently healthy subjects** (*Ho JE et al. JACC 2012; de Boer RA et al, Eur J Hear Fail 2013).*

Biomarkers in HCM: moving towards the future

In patients with HCM, Gal-3 may well be an ideal biomarker and may offer a particular window of opportunities:

- **to allow the identification of mutation carriers with early evidence of fibrosis preceding the development of LVH**
- **to contribute to widen the known risk profile of HCM patients already with the phenotype (establish fibrosis and hypertrophy) but before overt impairment of LV function**
- **to contribute to prognostic information, implying earlier treatment interventions**
- **Additionally the potential role of Gal-3 may include the chance to initiate targeted preventive treatment in the course of the *disease*** (*Azibani F et al. Hypertension 2012; Kawano H et al. Circ J 2005)*

Biomarkers in HCM: moving towards the future

- **At the Cardiomyopathies outpatient Unit of Santa Maria University Hospital (Lisboa), our team (that includes cardiologists and geneticists) follows regularly 120 families with HCM. The follow-up time of this population ranges from 1 to 38 years**

<u>Main purpose</u>:

- **To test the hypothesis that biomarkers of collagen turnover and additionally Gal-3 may be helpful in diagnosing HCM at the carrier state**

- **Literature is scarce regarding fibrosis biomarkers in HCM** *(Lombardi R et al. , Circulation 2003; Fassbach M et al. Z Kardiol 2005; Ho CY et al, NEJM 2010; de Boer RA et al, Eur J Heart Fail 2013)* **and data concerning Gal-3 are lacking**

- **In our investigation, the genetic status will be the gold standard**

Biomarkers in HCM: moving towards the future

- The biomarkers will be tested and compared in affected patients (LVH), relatives that are only-carriers (preclinical phase) and normal relatives
- Associations between biomarkers and the clinical status, genetics and morphological and functional cardiac imaging data will be undertaken
- The results may be of value if information afforded by biomarkers (Gal-3 in particular) or a combined strategy (biomarkers and imaging parameters) succeeds in the early identification of HCM (carrier state) therefore appearing as an alternative to the genetic diagnosis
- Additionally, a prospective longitudinal study of HCM patients and carriers, will give the opportunity to assess the prognostic role of Gal-3

Biomarkers in HCM: moving towards the future

- **In fact, the biomarker seems useful not only for the early detection of fibrosis but also for risk stratification, particularly in patients with diastolic HF to which fibrosis is a major pathophysiologic contributor** *(de Boer RA et al, Eur J Heart Fail 2013).*

Galectin-3 in heart failure with preserved ejection fraction

Rudolf A. de Boer[1]*, Frank Edelmann[2,3], Alain Cohen-Solal[4], Mamas A. Mamas[5], Alan Maisel[6], and Burkert Pieske[7,8]

Eur J Heart Fail 2013

- **Actually, this is the typical abnormality in patients with HCM …**

Biomarcadores de fibrose miocárdica na identificação precoce dos portadores de mocardiopatia hipertrófica.

Cronograma

Identificação da população

Avaliação cardiovascular
(exames complementares de diagnóstico)

Caracterização fenotípica

Obtenção do consentimento informado

Caracterização final da população (3 sub-grupos)
- Com fenotipo)
-Sem fenotipo (Genotipo + / Genotipo -)

Prenchimento do registo em papel e electrónico dos dados (Base de dados)

1- Avaliação laboratorial (inclui "rotinas" laboratoriais)
2- Colheita de sangue para biomarcadores de fibrose
3-Colheita de sangue para estudo genético

1- Resultado disponível em 24-48 horas (despiste de anomalia que implique a não-inclusão no estudo)
2- Tratamento e conservação das amostras para determinações posteriores (Biobanco)
3- Caracterização genética

Análise de resultados de biomarcadores

Análise de resultados genéticos e análises de co-segregação familiar

1 Março 2014 – 30 Novembro 2014

Dezembro 2014 – 28 Fev 2015

Análise estatística
Elaboração do relatório final

Biomarkers in Hypertrophic Cardiomyopathy:

moving towards the future

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Obrigada