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## **Myocardial stiffness evaluation using non-invasive shear wave imaging in healthy and hypertrophic cardiomyopathy adults**

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## ABSTRACT

**Objectives.** The goal of our study was to investigate the potential of Myocardial SWI to quantify the diastolic myocardial stiffness (MS, kPa) noninvasively in healthy adult volunteers (HV) and its physiological variation with age, and in hypertrophic cardiomyopathy populations with heart failure and preserved ejection function (HCM-HFpEF).

**Background.** Myocardial stiffness (MS) is an important prognostic and diagnostic parameter of the diastolic function. MS is affected by physiological changes but also by pathological alterations of extracellular and cellular tissues. However, the clinical assessment of MS and the diastolic function remains challenging. Shear wave imaging (SWI) is a novel ultrasound-based technique that has the potential to provide intrinsic MS noninvasively.

**Methods.** We prospectively included 80 adults: 60 HV (divided into three groups: 20-40 yo (n=20); 40-60 yo (n=20); 60-80 yo (n=20)) and 20 HCM-HFpEF. Echocardiography, cardiac magnetic resonance imaging (CMR) and biological explorations were achieved. MS evaluation was performed using an ultrafast ultrasound scanner with cardiac phased array. The fractional anisotropy (FA) of MS was also estimated.

**Results.** MS increased significantly with age in healthy volunteer (the mean MS was  $2.59\pm 0.58$ ,  $4.70\pm 0.88$  and  $6.08\pm 1.06$  kPa for the 20-40, 40-60, and 60-80 yo groups respectively,  $p<0.01$  between each group). MS was significantly higher in HCM-HFpEF patients than in healthy volunteer (mean MS= $12.68\pm 2.91$  kPa vs  $4.47\pm 1.68$  kPa,  $p<10^{-4}$ ), with a cut-off at 8 kPa (AUC=0.993, Se=95%, Sp=100%). The FA was lower in HCM-HFpEF (mean= $0.133\pm 0.073$ ) than in HV ( $0.238\pm 0.068$ ),  $p<0.01$ . Positive correlations were found between MS and diastolic parameters in echocardiography ( $E/e'$ ,  $r=0.783$ ;  $E/Vp$ ,  $r=0.616$ ; left atrial volume index,  $r=0.623$ ) and with fibrosis markers in CMR (late gadolinium enhancement,  $r=0.804$ , myocardial T1 pre-contrast,  $r=0.711$ ).

**Conclusion.** MS was found to increase with age in healthy adults and was significantly higher in HCM-HFpEF patients. Myocardial SWI has the potential to become a clinical tool for the diagnostic of diastolic dysfunction.

**CLINICAL TRIAL:** ClinicalTrials.gov: NCT02537041;  
<https://clinicaltrials.gov/ct2/show/NCT02537041>

**Key Words:** echocardiography • myocardial stiffness • myocardium • diastolic function

## ABBREVIATIONS:

**DT:** deceleration time

**ECV:** extracellular volume

**FA:** fractional anisotropy

**HCM:** hypertrophic cardiomyopathy

**HF:** heart failure

**HFpEF:** heart failure with preserved ejection function

**HV:** healthy volunteer

**IVRT:** isovolumic relaxation time

**LGE:** late gadolinium enhancement

**MS:** myocardial stiffness

**SWI:** shear wave imaging

**Vp:** transmitral flow propagation velocity;

## INTRODUCTION

Myocardial stiffness (MS) is known to play a key-role in diastolic left ventricular function (1).

Abnormalities in LV relaxation and MS are one of the key pathophysiological mechanisms (2) in heart failure patients with preserved ejection fraction (HFpEF). Hypertrophic cardiomyopathy is also associated to severe diastolic dysfunction mainly due to fibrosis and fiber disarray (3).

Moreover, MS is also affected by aging due to progressive physiological changes and cellular and extracellular matrix alterations. However, as the clinical assessment of MS and of the diastolic function is still challenging (4), the study of myocardial stiffness remained limited to invasive explorations (5).

In a general view, the assessments of diastolic function can be divided into those that reflect the process of active/auxotonic relaxation (depending on filling load and afterload) and those that reflect passive stiffness (independent of load conditions) (6). In clinical practice, biological parameters are correlated with ventricular filling pressures (brain natriuretic protein (7), BNP, for example), echocardiographic parameters are identified to assess the auxotonic relaxation and/or the filling pressure, and cardiac magnetic resonance imaging (CMR) offers tools to evaluate the myocardial fibrosis (late enhancement gadolinium (8), LGE) or the collagen volume fraction (pre-post contrast T1 mapping (9) or extracellular volume fraction (10), ECV). However, noninvasive estimation of passive stiffness remains challenging. To date, the cardiac catheterization is the only validated option to assess the passive stiffness clinically, through the compliance estimation thanks to the pressure-volume loops (11). But the risks for the patients, the necessary equipment and the costs of these interventions make this exam unfeasible in daily clinical practice.

Shear wave imaging (SWI) is an ultrasound-based technique for quantitative, local, and noninvasive mapping of soft tissue's stiffness. The clinical impact of SWI has been demonstrated during the last decade in the field of breast lesions (12) and liver (13) imaging. Quantification of MS using SWI has also been investigated extensively on animal models in previous studies (14). SWI was compared to invasive gold standard parameters (15) derived from Pressure-Volume loops and was shown to quantify the end-diastolic MS (i.e. passive stiffness) accurately. More recently, the clinical feasibility and reproducibility of transthoracic SWI was shown on a small group of healthy volunteer (16) and on pediatric patients (17). The next step is to demonstrate the clinical interest and contribution of this technology for the assessment of diastolic myocardial stiffness in adults and its impact on diastolic LV function. Unlike other imaging techniques, echocardiography is inexpensive, widely available and can be performed in real-time at the patient bedside allowing monitoring of the heart structure and function.

In this study, we aimed to perform the first clinical proof of concept of non-invasive myocardial stiffness evaluation on normal and pathological patients. More specifically, the goals of our study were 1) to quantify MS noninvasively with SWI in a healthy adult population in order to establish values of MS and its dependence with age, 2) to compare it to severely altered MS in hypertrophic cardiomyopathy (HCM) patients with HFpEF and 3) to investigate the correlation of MS with conventional echocardiography and CMR index of diastolic function.

## **METHODS**

### **Study patients & design**

This was a prospective study conducted at the Hôpital Européen Georges Pompidou, Paris, France. A population of healthy volunteers (HV) was contacted and recruited by the Clinical Investigation Center. HV specific inclusion criteria were: no history of heart failure symptoms,

LVEF >50%, E/e' <13, as well as normal values of brain natriuretic protein (BNP, <35 pg/ml).

Three age groups were composed within the recruited HV: 20 to 39 years old (yo), 40 to 59 yo, 60 to 79 yo. Exclusion criteria included systolic blood pressure (SBP)  $\geq$ 140mmHg or/and diastolic blood pressure (DBP)  $\geq$ 90mmHg, any persistent cardiac arrhythmia, more than moderate valvular disease, any relevant coronary artery diseases, any contraindication to cardiac magnetic resonance imaging (CMR), and anechogenicity.

Patients with clinical, genetic and echocardiographic evidence for sarcomeric HCM with HFpEF (HCM-HFpEF group) were included. HCM-HFpEF patients were identified according to the consensus of the European Society of Cardiology (18)(19), using specific inclusion criteria: wall thickness  $\geq$  15 mm in one or more LV myocardial segments; sarcomeric protein gene mutation identified; left ventricular ejection fraction (LVEF) >50%; New York Heart Association functional class  $\geq$ II; at least one hospitalization for acute heart failure; and E/e'  $\geq$ 13 or E/e' 8 to 13 combined with elevated BNP (>35 pg/ml).

All subjects included in the study underwent clinical explorations, biological explorations (hematocrit, CRP, BNP), an echocardiography, a CMR and a cardiac SWI. All explorations were performed on the same day. Three months later and if no clinical event was noted (symptoms of heart failure, hospitalization for cardiac cause, modification of weight or BP), a second echocardiography and cardiac SWI were realized to estimate the reproducibility on five patients per HV sub-group, randomly selected (n total = 15).

The study was approved by the local ethics committee, and all patients gave written informed consent (Non-Invasive Evaluation of Myocardial Stiffness by Elastography; this trial is registered with ClinicalTrials.gov, NCT02537041).

### **Imaging procedures**

### *Echocardiography*

Echocardiographic explorations were performed on a Vivid 9 system (General Electric Healthcare, Chalfont St. Giles, Great Britain). Mitral valve inflow pattern (E and A velocity), E-wave deceleration time (E-wave DT), isovolumic relaxation time (IVRT), transmitral flow propagation velocity (Vp), septal mitral valve annular velocities (e' and a'), as well as pulmonary veins S-wave on D-wave ratio (PV S/D ratio) were recorded in an apical 4-chamber view, to assess the markers of diastolic function according to American Society of Echocardiography guidelines (20). Global and septal longitudinal strain was also performed by the Speckle Tracking 2D Strain software of General Electrics, directly on the Vivid 9 system. Data were analyzed from stored images by experienced operators (O.V. and A.H.) who were unaware of other test results. Measurements were made over 3 cardiac cycles; the average was used for statistical analysis.

### *CMR*

The CMR protocol consisted of cine-sequences, T1-weighted spin-echo, and 2-dimensional inversion recovery gradient echo sequences for late enhancement assessment after gadobutrol administration (LGE). Post contrast T1 times (T1 mapping) was performed with a modified Look-Locker inversion recovery sequence with a 3(3)5 scheme before and 15 min after contrast application (21). Mapping was performed over all available short-axis slices. Extracellular volume fraction (ECV) was calculated on the basis of the combination of pre- and post-contrast T1 mapping data according to the approach proposed by Rommel et al. (10). All acquisitions were consistent with the Society for Cardiovascular Magnetic Resonance published guidelines (22). Data were interpreted by two experienced readers (E.M. and G.S.) who were unaware of the subjects' clinical information and the results of other diagnostic tests.

### *Myocardial stiffness measured by shear wave imaging (figure 1 and video online)*

SWI is based on the remote generation of shear waves in soft tissue by acoustic radiation force combined with ultrasonic ultrafast imaging of the shear wave propagation (5000 images/s), using the same ultrasonic transducer (23). This modality has already been described in previous works (14)(15), and is also described in more details in the supplementary methods. In this study, a phased array probe (2.75-MHz central frequency; SuperSonic Imagine, Aix-en-Provence, France) connected to an ultrafast ultrasound scanner (Aixplorer, SuperSonic Imagine, Aix-en-Provence, France) was used. A conventional real-time echocardiographic image was used to position the probe. The focus of the acoustic radiation force generation was adjusted manually by the operator on the myocardial wall. The operator then launched the SWI acquisition that lasted approximately one second.

The explored myocardial segment was the antero septo basal segment (ASB segment). It was evaluated in two orthogonal axes (short- and long-axis views, see figure 1). Short-axis measurements were used to derive the shear modulus, whereas long-axis and short-axis values were used to compute the fractional anisotropy. All acquisitions were performed at end-diastole and triggered by an electrocardiogram (ECG). The thirty frames recorded after the push were post-processed to visualize the shear wave and compute the speed.

Data were interpreted off-line by one experienced reader (O.V.) who was unaware of the subjects' clinical information and the results of other diagnostic tests.

### *Fractional Anisotropy*

Like any fiber-composed muscular tissue, the myocardium presents a significant anisotropy of its elastic properties. Consequently, MS is expected to be higher when measured along the fibers, which are mainly oriented along the circumferential direction in the mid-wall layer. In order to



evaluate the degree of anisotropy in the myocardium, the fractional anisotropy (FA) was computed. FA was defined using two shear wave speed (SWS) measurements performed in orthogonal propagation directions (long axis and short axis views) using the formula published by Lee et al. (24). More details on the method are given in the supplementary methods.

### **Statistical analysis**

Data for continuous variables are presented as mean  $\pm$  SD, if normally distributed, or as median and interquartile range if non-normally distributed. Categorical variables are presented as frequencies and percentages. Comparisons between groups were made using chi-square tests for categorical variables. Continuous variables were compared with unpaired Student t tests or the nonparametric Mann-Whitney U test where appropriate. Univariate and stepwise multivariate linear regression analyses were performed to identify predictors of r (standardized coefficient of linear regression). Receiver operating characteristic (ROC) curves and area under the curve (AUC) were computed to assess the effectiveness of MS to predict healthy or pathologic subjects. Reproducibility of MS estimation (three months after the first estimation) was tested by the Bland-Altman limits of agreement. The reproducibility coefficient was calculated as 1.96 x the SD of the differences, as proposed by Bland and Altman(25). All the analyses were conducted using *Medcalc* (MedCalc Software, Mariakerke, Belgium).

## **RESULTS**

### **Population characteristics**

A total of 93 subjects (69 HV and 24 HCM-HFpEF) were prospectively screened for inclusion into the study (see figure 2, Flowchart). Eight patients of the HV group were excluded based on the exclusion criteria (1 congenital heart disease and 1 valvulopathy on echocardiography, 1 doubt on infarct scar on CMR, 6 anechoic). Two patients of the HCM-HFpEF group were

excluded based on the exclusion criteria (2 infarct scars seen on CMR, 2 anechoic). Finally, 80 subjects were included: HCM-HFpEF group (n=20), HV 20-39 yo group (n=20), HV 40-59 yo group (n=20), HV 60-79 yo group (n=20). See the flowchart in figure 2.

The molecular genetic causes of HCM-HFpEF group were: 8 mutations of MYH7, 6 mutations of MYBPC3, 2 mutations of TNNT2, 1 mutation of TPM1, 1 mutation of TNNT3, 1 mutation of MYL3, 1 mutation of MYL2.

Subjects' baseline characteristics including clinical characteristics, laboratory data, echocardiographic results, and CMR results are shown in table 1.

There is no statistical difference between the HV group and the HCM-HFpEF group in terms of age (p=0.22), BMI (p=0.74), and BP (systolic, p=0.41; diastolic, p=0.47). In both groups, there was no diabetic patient.

Concerning the HCM-HFpEF group, 6 patients (30%) had a NYHA functional class  $\geq$ III (4=III, 2=IV). 20 patients (100%) had a BNP >35 pg/ml. Regarding echocardiographic results, LV mass index was significantly higher than the HV group ( $125\pm 34$  versus  $70.6\pm 20$ , p<0.01), the ASB segment was significantly thicker than the HV group ( $20.8\pm 5.1$  versus  $5.9\pm 1.4$ , p<0.01), with a segment strain lower than the HV group ( $-6.4\pm 3.6$  versus  $-16.9\pm 2.2$ , p<0.01). All the main diastolic function parameters were significantly different (p<0.01) than those of the HV group (E/A; e'; E/e'; E-wave DT; IVRT; Vp; E/Vp, PV S/D ratio). Regarding CMR results, 16/20 (80%) had a LGE on the ASB segment (p<0.01). There was a difference between HV and HCM-HFpEF groups concerning myocardial T1 post-contrast (p=0.02) and ECV (p<0.01).

### **Myocardial stiffness results**

#### ***HV group (figure 3)***

The mean MS of HV group was  $4.47\pm 1.68$  kPa. No HV people had a MS value over 8 kPa. The mean MS was  $2.59\pm 0.58$  kPa for the 20-39 yo HV group,  $4.70\pm 0.88$  kPa for the 40-59 yo HV group, and  $6.08\pm 1.06$  kPa for the 60-79 yo HV group. There was a statistical significant difference between all age group ( $p<0.01$ ).

#### *Myocardial stiffness dependence on age*

A strong increase in MS with age was found (Figure 3). The correlation between age (x) and MS (y) values was robust ( $y=0.087x+0.1248$ ,  $r^2=0.77$ ,  $p<0.01$ ). A multivariate linear regression analysis (including sex, age, BMI, HR, SBP, DBP) showed age was the only clinical parameter correlated with the MS (age,  $p<0.01$ ; sex,  $p=0.77$ ; BMI,  $p=0.98$ ; HR,  $p=0.88$ ; SBP,  $p=0.33$ ; DBP,  $p=0.63$ ). The correlation of echocardiographic parameters and age was lower: E/A,  $r^2=0.30$ ; E/e',  $r^2=0.23$ ; E/Vp  $r^2=0.01$  (see supplementary figure A). In univariate analysis for the HV group, there was no correlation between LV mass and MS ( $r=0.21$ ,  $p=0.44$ ).

#### *HCM-HFpEF group*

The mean MS of the HCM-HFpEF group was  $12.68\pm 2.91$  kPa. Only two patients had a MS value under 8 kPa (6.46 and 7.97 kPa). The correlation between age and MS values for this pathological group was low ( $r^2=0.14$ ,  $r=0.37$ ,  $p<0.01$ ). We found no difference between MYH7 and MYBPC3 mutation subgroups ( $p=0.34$ ).

#### *Comparison between MS healthy and MS HCM-HFpEF groups (figure 4)*

There was a significant statistical difference between the MS healthy group and the MS HCM-HFpEF group ( $p<0.01$ ). Based on the ROC curve analysis, the optimal cut-off value of MS for detection of HCM-HFpEF was 8 kPa (AUC=0.993, Se=95%, Sp=100%).

#### *Correlation of MS with measures of diastolic function and others parameters*

Positive correlations were found between MS and parameters in echocardiography ( $E/e'$ ,  $r=0.783$ ,  $p<0.01$ ;  $E/Vp$ ,  $r=0.616$ ,  $p<0.01$ ; left atrial volume index,  $r=0.623$ ,  $p<0.01$ ) and CMR (LGE,  $r=0.804$ ,  $p<0.01$ ; myocardial T1 pre-contrast,  $r=0.711$ ,  $p<0.01$ ; myocardial T1 post-contrast,  $r=0.595$ ,  $p=0.01$ ; ECVF fraction,  $r=0.447$ ,  $p=0.03$ ). All the correlation of MS with others parameters are summarized in table 2. There was no correlation between MS and the global strain ( $r=0.37$ ,  $p=0.27$ ) or the septal strain ( $r=0.4$ ,  $p=0.09$ ). There was no correlation between MS and BNP ( $r=0.41$ ,  $p=0.06$ ).

### ***Reproducibility***

On the fifteen HV reevaluated three months later, there was no statistical difference with the initial assessment (mean MS =  $4.26\pm 1.36$  kPa,  $p=0.67$ ). Moreover, Bland-Altman analysis demonstrated good agreement between measurements: MS +0.08 kPa (upper limit of agreement [ULA]: +0.89 kPa; lower limit of agreement [LLA]: -0.73 kPa), see supplementary figure B.

### **Fractional anisotropy (figure 5)**

The mean fractional anisotropy of the HV group ( $0.238\pm 0.068$ ) was higher than that of the HCM-HFpEF group ( $0.133\pm 0.073$ ,  $p<0.01$ ). 18/20 (90%) patients in HCM-HFpEF group had a fractional anisotropy under 0.155 while 56/60 (93%) HV had a fractional anisotropy over this cut-off (AUC=0.891, Sensibility=90%, Specificity=91.2%).

## **DISCUSSION**

In this study, MS was assessed quantitatively using non-invasive SWI in HV and HCM patients with HFpEF. To our knowledge, this is the first study to assess MS quantitatively and noninvasively in both HV and pathological cases (HCM-HFpEF). The main results of the study were: 1) SWI allowed us to establish values of MS in a healthy volunteer population; 2) MS was

found to increase strongly with age in the normal heart; 3) there was a large difference in myocardial stiffness between HV and HCM-HFpEF (cut-off =8 kPa).

An important result of this study is the quantification of the myocardial stiffness aging. In the NORRE Study (26), Caballero et al. also found a gradual change with age of the main echocardiographic parameters of the diastolic function. In this study, which analyzed 449 HV echocardiographs, the E/e' ratio increased from an average  $6.9 \pm 1.6$  in 20-40 yo subjects to an average  $9.7 \pm 2.8$  in 60-75 yo subjects, a change of approximately 50% with a fairly linear evolution. This myocardial aging was also evaluated by CMR on human population (27) or by invasive estimation on animal study (28). In 1991, Weger et al have well demonstrated that the age-induced physiological myocardial fibrosis impacts on the cardiac function (29), including the ability of the ventricle to relax during the diastolic filling (auxotonic relaxation). Regarding HV who participated in our study, we also found a linear evolution of myocardial stiffness, allowing to establish the change of MS with age.

The second interest of our study was to demonstrate a myocardial stiffness difference between HV and HCM-HFpEF noninvasively. Zile et al have shown on myocardial histologic explorations of HFpEF patients (30) that an increase in passive myocardial stiffness is due to an architectural modification (increase of collagen and titin). Moreover, in a systematic review on HCM (3) published in 2002, Barry J. Maron noted that the "LV myocardial architecture is disorganized [...] with multiples intercellular connections often arranged on chaotic alignment and with expanded interstitial (matrix) collagen", which is supported by previous work which tried to link myocardial histological explorations and myocardial stiffness (31). Our study shows that the abnormal myocardial stiffness of this characteristic pathological group (HCM-HFpEF) can be quantified noninvasively. In addition, SWI provided also information on the myocardial

architecture through the analysis of the fractional anisotropy which revealed differences between the tissue architecture of the two groups, with a decrease of the physiological anisotropy in the HCM-HFpEF group. The clinical interest of this parameter needs however to be further investigated and analyzed on more patients and other pathological groups.

Beyond the analysis of viscoelastic properties and of tissue structure, the comparison of MS with the recommended ultrasound parameters used to assess the diastolic function seems to show that this quantitative parameter could help to distinguish patients with diastolic dysfunction from others. Obviously, the diastolic function analysis remains complex and it would be unrealistic to think that one quantitative parameter could define the left ventricular diastolic function. For example, LAVI  $>34\text{ml/m}^2$  is one of the key structural alteration allowing the definition the diagnostic of HFpEF (19), but Caballero et al (26) have also clarified that 15.1% of healthy people have a LAVI  $>34\text{ml/m}^2$  while only 0.5% have a  $E/e'$  ratio  $>15$ . Nevertheless, the MS assessment of patients with HFpEF has clearly helped to understand this disease better (32). Being able to perform it noninvasively would refine our diagnostic capabilities and probably would help us to understand disease “at the bedside”, with a noninvasive approach.

Beyond the diagnostic contribution that the evaluation of MS by SWI could represent, the prospects of therapeutic follow-up could be interesting. The current finding is that there is no specific medical treatment of diastolic dysfunction in HCM. This is probably due to the fact that there is as yet no medical treatment with a high expected efficacy in HFpEF, as recalled in the recent European guidelines: “No treatment has yet been shown, convincingly, to reduce morbidity or mortality in patients with HFpEF” (19). Noninvasive MS assessment could be a major tool for the development of novel treatments of HCM and/or HFpEF. Thanks to this noninvasive myocardial stiffness marker, the impact of certain treatments (angiotensin-

converting enzyme inhibitors or mineralocorticoid / aldosterone receptor antagonists for example) could be evaluated quantitatively.

Finally, we have observed a good reproducibility of the MS assessment. Despite the small size of this analysis group (n=15), which limits its interpretation, these results indicate that this technique could be used to evaluate a patient through a longitudinal follow up. We did not reevaluate the reproducibility of this technique on HCM-HFpEF groups for two reasons: 1) it is still difficult to estimate the impact of the disease evolution on the MS results, 2) the treatment of these patients were modified after the initial evaluation and could modify their diastolic function (and maybe their myocardial structure).

### **Limitations**

This was a monocentric study, and on a small sample. It is therefore difficult to extrapolate these results to a general population, which would require larger population groups. The gold standard of MS assessment remains an invasive measurement with a conductance catheter. From a regulatory point-of-view, this exploration could not be achieved on healthy volunteers recruited exclusively for this study, notably because of the risks inherent to this invasive exploration.

However, previous work on animal model had shown a strong correlation between MS estimated by SWI and MS estimated through the end-diastolic strain-stress relationship(15)(14). In addition, the non-invasive echocardiographic evaluation of myocardial stiffness has been shown possible by extrapolating the Left Ventricular Volume-Pressure Curve (EDPVR), knowing a single-beat (single-beat) point, based on Doppler and bidimensional data (volume) (33)(34)(35).

It will be interesting in future studies to compare the MS estimated by SWI with this non-invasive method. Concerning the HCM-HFpEF group, no catheterization was provided in the management of these patients during the time of the study. The second limitation of our study is

the local evaluation of MS by the SWI. Indeed, we compared global functional parameter ( $E/e'$ ,  $E/Vp$  or LAVI) with a segmental parameter (myocardial stiffness of the ASB segment).

Nonetheless, the same segment was analyzed for all people included in the study. This study was limited to the basal septum. The main reason is that we used a conventional phased array with an elevation focus at 70mm which limited the generation of the shear waves at higher depth. In order to address other segments, the development of dedicated probes will be required.

## **CONCLUSION**

In this study, we quantitatively assessed the end-diastolic myocardial stiffness in humans adults using SWI in healthy volunteers and sarcomeric hypertrophic cardiomyopathies with HFpEF patients. The myocardial stiffness was found to increase with age and a cut-off of 8 kPa allowed differentiating clearly these two groups. The fractional anisotropy obtained by SWI reflected the underlying tissue structure modifications. Thanks to this ultrasound technology, the noninvasive assessment of myocardial stiffness enables a new diagnostic option in cardiology. Future studies will aim to evaluate MS on other heart diseases, such as isolated HFpEF, HFrEF, hypertension, diabetes cases with HFpEF, or other cardiomyopathies in order to determine the impact of this parameter in clinical practice.



## **CLINICAL PERSPECTIVES**

### **Competency in Medical Knowledge**

This study is the first, to our knowledge, to quantify myocardial stiffness in patients using non-invasive Shear wave imaging. It opens the path to the clinical evaluation of LV function using a new parameter relatively independent of loading. We expect this parameter to be robust, stable and representative of the myocardial LV diastolic function.

### **Translational outlook**

Future studies should address the evaluation of this new parameter in systolic and diastolic heart failure patients and whether this parameter could improve the diagnosis and prognosis of this population.

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## **FIGURE LEGENDS**

### **Figure 1: Myocardial Shear Wave Imaging**

*B-mode and Shear wave elastography imaging examples of a Healthy Volunteer (HV). Shear wave propagation in short- and long-axis views of a HV (Tissue axial velocity images).*

### **Figure 2: Study Flowchart**

The study was performed on 60 healthy volunteer and 20 HCM patients.

### **Figure 3: Myocardial Stiffness for Healthy Volunteer**

Myocardial stiffness measured in HV as a function of age.

### **Figure 4: Myocardial stiffness in HCM and HV groups**

Comparison of Myocardial Stiffness between healthy volunteer group (HV) and hypertrophic cardiomyopathy with HFpEF group (HCM group)

### **Figure 5: Fractional Anisotropy**

Comparison of Fractional Anisotropy between healthy volunteer group (HV) and hypertrophic cardiomyopathy with HFpEF group (HCM group)

## TABLES

Table 1. Population characteristics

	<b>Healthy volunteer (n=60)</b>	<b>HCM-HFpEF (n=20)</b>	<b>p</b>
Age (years)	50.6±16.9	57±17.5	0.22
Sex (M/F)	31/29	17/3	<b>&lt;0.01</b>
BMI (kg/m <sup>2</sup> )	23.6±2.9	24.8±3.6	0.74
Systolic BP, mmHg	117±10	115±11	0.41
Diastolic BP, mmHg	70±7	75±6	0.47
NYHA I	52	0	<b>&lt;0.01</b>
NYHA II	8	14	<b>&lt;0.01</b>
NYHA III-IV	0	6	<b>&lt;0.01</b>
<b>Biology (blood explorations)</b>			
CRP (mg/l)	1.4±1.1	1.9±0.8	0.55
BNP (pg/ml)	16 [ $<5-29$ ]	365 [183-512]	<b>&lt;0.01</b>
Hematocrit (%)	43 (41-45)	40 (38-42)	<b>0.03</b>
<b>Echocardiography parameters</b>			
LA surface (4 cavities view, cm <sup>2</sup> )	16.1±4	29.3±7.1	<b>&lt;0.01</b>
LAVI (ml/m <sup>2</sup> )	25.9±8.7	43.3±18.6	<b>&lt;0.01</b>
LAVI >34ml/m <sup>2</sup>	12/60 (20%)	15/20 (75%)	<b>&lt;0.01</b>
LVEF (%)	68±9.9	66±7.9	0.67
LVEDD	45.9±4.8	49.9±5.7	0.47

LVESD	28.3±4.8	24.6±3.2	0.22
LV Mass / BSA (g/m <sup>2</sup> )	70.6±20	125±34	<b>&lt;0.01</b>
LV GS (%)	17.4±2.4	14.6±3.1	<b>&lt;0.01</b>
ASB segment GS (%)	16.9±2.2	6.4±3.6	<b>&lt;0.01</b>
ASB segment end diastolic thickness (mm)	5.9±1.4	20.8±5.1	<b>&lt;0.01</b>
Peak E-wave (cm/s)	74.8±17.6	88.3±30.2	<b>&lt;0.01</b>
E/A	1.4±0.5	1.1±0.4	<b>&lt;0.01</b>
e' septal (cm/s)	13.8±4.1	5.8±1.9	<b>&lt;0.01</b>
E/e'	5.9±2.4	16.1±6.5	<b>&lt;0.01</b>
e'/a' septal	1.6±0.8	1.3±0.9	0.29
E-wave DT (ms)	179±60	238±62	<b>&lt;0.01</b>
IVRT (ms)	94±17	144±31	<b>&lt;0.01</b>
Vp (cm/s)	50.4±7.4	29.2±5.5	<b>&lt;0.01</b>
E/Vp	1.3±0.3	3.4±1.5	<b>&lt;0.01</b>
PV S/D ratio	1.2±0.3	0.7±0.3	<b>&lt;0.01</b>
<b>Cardiac Magnetic Resonance</b>			
ASB segment end diastolic thickness (mm)	5.7±1.4	18.3±3.4	<b>&lt;0.01</b>



LV mass / LVED volume (g/ml)	0.75±0.17	2.1±0.51	<b>&lt;0.01</b>
Myocardial T1 pre-contrast (ms)	1217±49	1299±80	<b>&lt;0.01</b>
Blood T1 pre-contrast (ms)	1738±102	1694±67	0.17
Myocardial T1 post-contrast (ms)	440±52	395±60	<b>0.02</b>
Blood T1 post-contrast (ms)	247±41	230±50	0.08
Focal LGE present (ASB segment)	0/60 (0%)	16/20 (80%)	<b>&lt;0.01</b>
Extracellular volume fraction (%)	24.5±3.7	27.2±4.1	<b>&lt;0.01</b>

**A:** late diastolic peak (pulsed-wave doppler); **a’:** late diastolic mitral annular velocity by doppler tissue imaging; **ASB:** antero septo basal; **BSA:** body surface area; **CRP:** **DT:** deceleration time; **E:** early diastolic peak (pulsed-wave doppler); **e’:** early diastolic mitral annular velocity by doppler tissue imaging; **GS:** global strain; **IVRT:** isovolumic relaxation time; **LA:** left atrium; **LAVI:** left atrium volume index; **LVEF:** left ventricle ejection fraction; **LVEDD:** left ventricle end-diastolic diameter; **LVESD:** left ventricle end-systolic diameter; **NTproBNP:** N-terminal pro brain natriuretic peptide ; **PV S/D ratio :** pulmonary veins velocities **Vp:** transmitral flow propagation velocity;

**Table 2. Myocardial Stiffness correlations.**

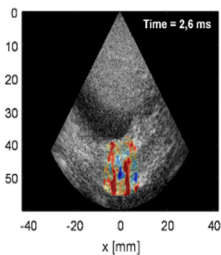
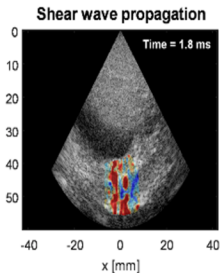
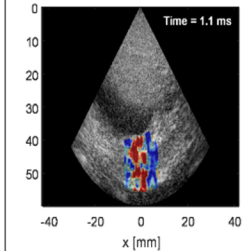
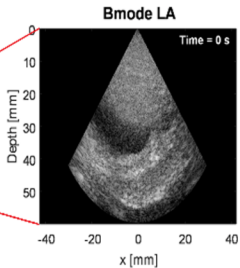
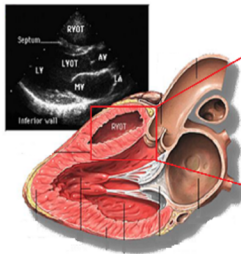
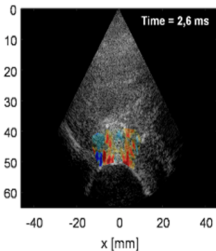
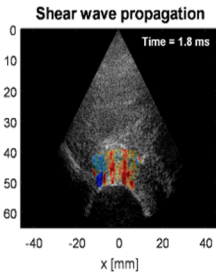
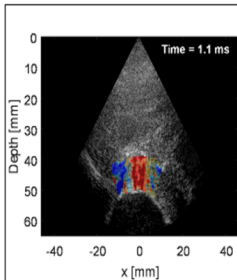
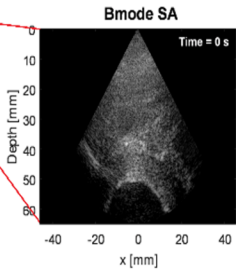
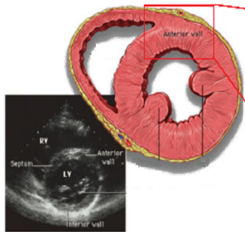
	<b>r</b>	<b>p</b>
Age (years)	<b>0.881</b>	<b>&lt;0.01</b>
Sex (M/F)	NA	NA
BMI (kg/m <sup>2</sup> )	0.089	0.98
Systolic BP, mmHg	0.207	0.33
Diastolic BP, mmHg	0.154	0.63
NYHA class	<b>0.677</b>	<b>0.02</b>
<b>Biology (blood explorations)</b>		
CRP (mg/l)	0.217	0.36
BNP (pg/ml)	0.413	0.06
Hemotacrit (%)	0.299	0.15
<b>Echocardiography parameters</b>		
LA surface (4 cavities view, cm <sup>2</sup> )	0.378	0.21
LAVI (ml/m <sup>2</sup> )	<b>0.623</b>	<b>&lt;0.01</b>
LVEF (%)	0.204	0.45
LVEDD	0.266	0.51
LVESD	0.178	0.76
LV Mass / BSA (g/m <sup>2</sup> )	0.329	0.23
LV GS (%)	0.378	0.27
ASB segment GS	0.420	0.09

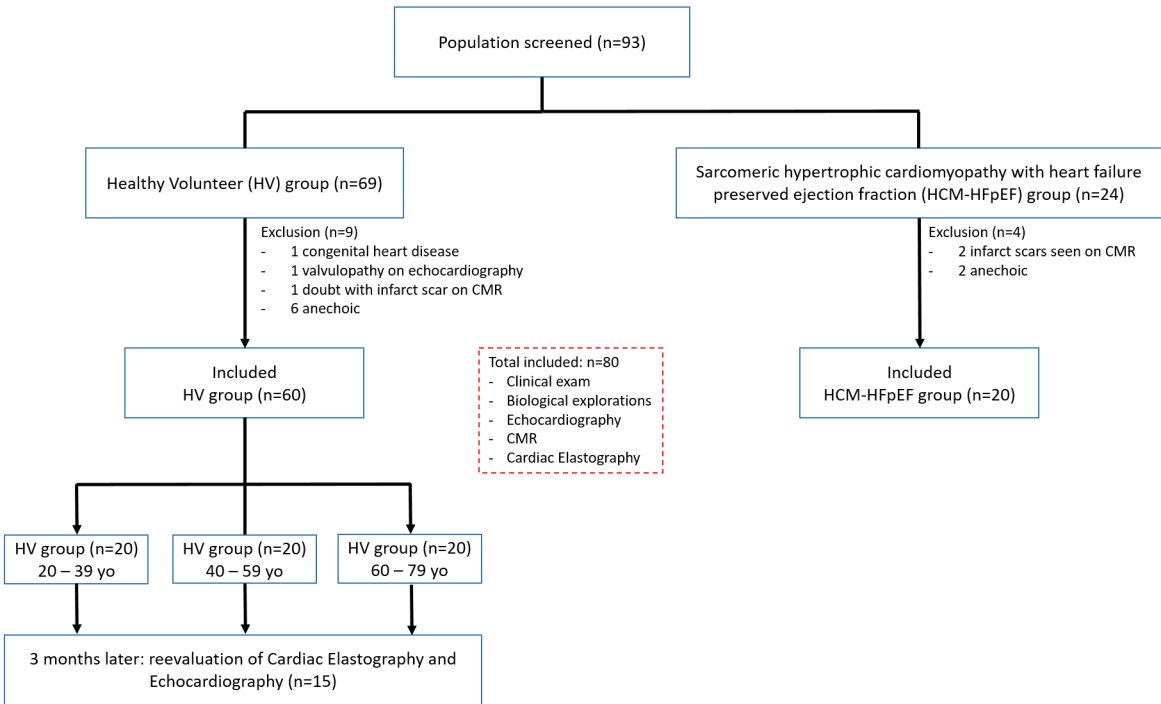
(%)		
ASB segment end diastolic thickness (mm)	0.277	0.31
Peak E-wave (cm/s)	0.304	0.30
E/A	<b>0.506</b>	<b>0.01</b>
e' septal (cm/s)	0.365	0.39
E/e'	<b>0.783</b>	<b>&lt;0.01</b>
e'/a' septal	0.452	0.07
E-wave DT (ms)	<b>0.511</b>	<b>0.02</b>
IVRT (ms)	0.361	0.14
Vp (cm/s)	0.219	0.55
E/Vp	<b>0.616</b>	<b>&lt;0.01</b>
PV S/D ratio	0.422	0.10
<b>Cardiac Magnetic Resonance</b>		
ASB segment end diastolic thickness (mm)	0.325	0.17
LV mass / LVED volume (g/ml)	0.388	0.11
Myocardial T1 pre-contrast (ms)	<b>0.711</b>	<b>&lt;0.01</b>
Blood T1 pre-	0.195	0.67

contrast (ms)		
Myocardial T1 post-contrast (ms)	<b>0.595</b>	<b>0.01</b>
Blood T1 post-contrast (ms)	0.101	0.77
Focal LGE present (ASB segment)	<b>0.804</b>	<b>&lt;0.01</b>
Extracellular volume fraction (%)	<b>0.447</b>	<b>0.03</b>

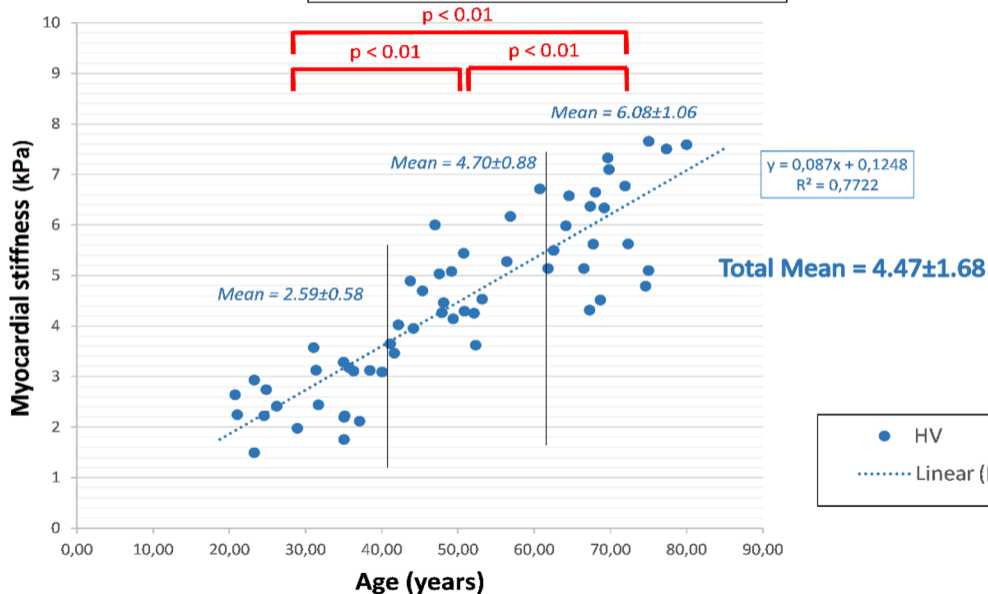
**A:** late diastolic peak (pulsed-wave doppler); **a':** late diastolic mitral annular velocity by doppler tissue imaging; **ASB:** antero septo basal; **BSA:** body surface area; **CRP:** **DT:** deceleration time; **E:** early diastolic peak (pulsed-wave doppler); **e':** early diastolic mitral annular velocity by doppler tissue imaging; **GS:** global strain; **IVRT:** isovolumic relaxation time; **LA:** left atrium; **LAVI:** left atrium volume index; **LVEF:** left ventricle ejection fraction; **LVEDD:** left ventricle end-diastolic diameter; **LVESD:** left ventricle end-systolic diameter; **NTproBNP:** N-terminal pro brain natriuretic peptide ; **PV S/D ratio :** pulmonary veins velocities **Vp:** transmitral flow propagation velocity;

**Video 1:** Shear wave propagation in a human heart.



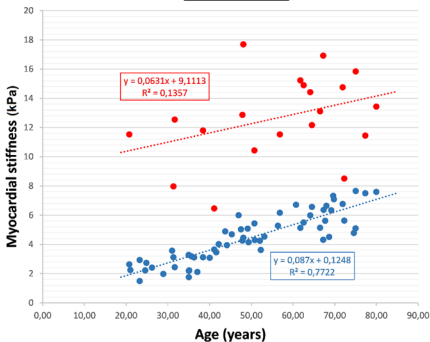


# Myocardial Stiffness - Healthy Volunteer





### HV versus HCM

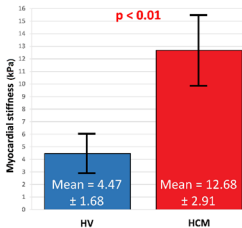


Mean = 12,68±2.91

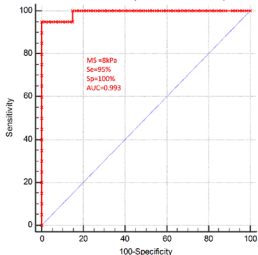
**$p < 0.01$**

Mean = 4.47±1.68

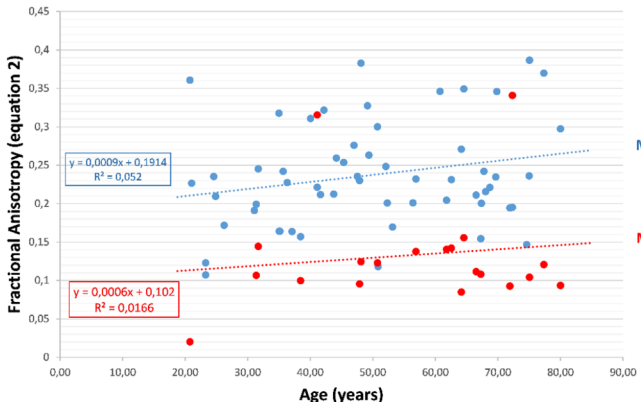
### HV versus HCM



### ROC curves for Healthy volunteer and HCM-HFpEF



Fractional Anisotropy of HV and HCM



Mean =  $0.238 \pm 0.068$

$p < 0.01$

Mean =  $0.133 \pm 0.073$

- HV
- HCM
- ..... Linear (HV)
- ..... Linear (HCM)

FA - HV versus HCM

