PEER REVIEW HISTORY

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ARTICLE DETAILS

| TITLE (PROVISIONAL) | How does morphology impact on diastolic function in hypertrophic cardiomyopathy? A single center experience. |
|---------------------|----------------------------------------------------------------------------------------------------------|
| AUTHORS             | Finocchiaro, Gherardo; Haddad, Francois; Pavlovic, Aleksandra; Magavern, Emma; Sinagra, Gianfranco; Knowles, Joshua W.; Myers, Jonathan; Ashley, Euan |

VERSION 1 - REVIEW

| REVIEWER            | Ashraf M Anwar |
|---------------------|----------------|
| Cardiology Department, KFAFH, Jeddah, Saudi Arabia |

| REVIEW RETURNED     | 27-Feb-2014 |

| GENERAL COMMENTS    | The manuscript included good number of HCM patients and aimed to describe diastolic dysfunction in subgroups of HCM. There are many major points need response. 1. Method section is missed, some sentences in the introduction, some mentioned in the result. You need to separate it under method section 2. What is the inclusion and exclusion criteria? For example, no HCM patients with AF, no HCM patient underwent intervention (PTSMA or surgical myectomy)........etc 3. Number of patients in HCM group and control group mentioned in abstract only not in the text. Also number of patients in each subgroup of HCM mentioned in the table but not inside the text. 4. Grading of diastolic dysfunction was not considered for comparison. It was better to classify patients according to the grades of diastolic dysfunction, then compare the subgroup of HCM based on this grades. 5. By PWD, the mean of E velocity, A velocity, E/A ratio will not reflect anything either in HCM patients or controls due to the changes occur from grade of diastolic dysfunction to another 6. Significant LVOT gradient was detected in apical HCM. Do you have any explanation because the thickness only involve the apex not the septum. 7. One of the study limitation is calculation of LV mass because the MRI data was not available to all patients. If you have data for a considerable number of patients you can include and correlate with the severity of dystolic dysfunction. 8. RV dysfunction was detected in 31 HCM patients. Do you have any explanation especially with normal or supernormal LV systolic function?. What is the parameter you relied on for the diagnosis of RV dysfunction?. RVFAC was normal in both HCM and control groups 9. TAPSe was mentioned in the last paragraph of introduction. Nothing about it in the result section. 10. RA volume was inserted for comparison in table2. It was not mentioned as a method and also in result section 11. It was better to describe LA function (passive and active) rather |
To investigate the relationship between morphology and left ventricular diastolic dysfunction in patients with hypertrophic cardiomyopathy (HCM), the authors have evaluated LV diastolic function in HCM patients (n=383) with various morphological patterns and normal subjects by using echocardiography. They found that LV diastolic dysfunction in HCM is equally present irrespective of different pattern of hypertrophy. They also demonstrated that LV diastolic dysfunction in HCM is significantly associated with LV outflow obstruction, age, degree of mitral regurgitation (MR) and intraventricular septal thickness (IVS).

This is an interesting and well written paper. However, the authors should address issues described below;

In this study authors measured mitral valve inflow velocity (E and A wave velocity) and peak myocardial early diastolic velocity at the lateral mitral annulus (lateral E' wave velocity) for evaluation of LV diastolic dysfunction. However, it is well known that E and A wave velocity, as well as E' velocity and thus E'/E ratio, are affected by ventricular loading condition such as preload, although TDI velocities are less influenced by loading conditions. In addition, both E and E' velocity are also increased in patients with moderate to severe mitral regurgitation, which may be associated with increased preload.

Indeed, LV outflow obstruction in HCM is usually accompanied by some degree of mitral regurgitation. Therefore, all of the presence of mitral regurgitation (n=134), moderate to severe mitral regurgitation (n=24) and usage of diuretics (n=50) might modify mitral valve inflow velocity and peak myocardial early diastolic velocity. To exclude these possibilities, authors should also investigate diastolic function in HCM patients without LV outflow obstruction (>30mmHg), moderate to severe mitral regurgitation or diuretics usage for the purpose of this study.

1. The authors should identify how many HCM patients were in the database from 1999 to 2011, and how many were screened and excluded for each/very exclusion criterion to give readers an idea of the generalizability of the data.
2. What was the rationale for including a control population? Would not each morphological HCM type serve as a comparator to the other?
3. The authors should provide an actual echocardiographic 2D image of each morphological HCM type described on page 5, paragraph 4.
4. 2D and m-mode measurements and cut-off values for LV hypertrophy, as detailed in the ASE 2005 Chamber Quantification Guidelines, have different cut-off values. Can the authors show, perhaps in table, how these different values were handled and how
they were applied to the study population?

5. Why was only lateral e' measured?

6. The Results section has too many numbers and is difficult to read (especially with OR data). In general, detailed numbers can be presented in tables and figures and the Results section should not repeated these data but provide overall findings and trends while referring to tables and figures.

7. Do the authors have any clinical data (development of clinical HF, hospitalization for HF, incidence of AF, VT, death) that they could correlate with the diastolic variables/morphological HCM type?

8. Are any BNP or NT-proBNP data available to correlate with the diastolic indices?

9. Are any invasive hemodynamic data available to corroborate the diastolic findings in this study?

10. More detail, analysis and discussion of the relation of diastolic function and genetic markers is warranted.

11. The Limitations section can be expanded to cover some of the issues raised above.

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1

The manuscript included good number of HCM patients and aimed to describe diastolic dysfunction in subgroups of HCM. There are many major points need response.

1. Method section is missed. some sentences in the introduction, some mentioned in the result. You need to separate it under method section

**ANSWER:** Done. Now there are no "methods sentences" in the introduction or in the results.

2. What is the inclusion and exclusion criteria?. For example, no HCM patients with AF, no HCM patient underwent intervesion (PTSMA or surgical myectomy).......etc

**ANSWER:** PATIENTS WERE CONSECUTIVELY ENROLLED IN THE STANFORD HCM DATABASE. FOR THIS STUDY WE RETROSPECTEVELY ANALYZED THE PATIENTS WITH NORMAL SYSTOLIC FUNCTION (DEFINED BY EF>55%) AND IN SINUS RIGTHM AT THE MOMENT OF THE EXAM. WE DIDN'T EXCLUDE OTHER PATIENTS. SOME PATIENTS UNDERWENT INTERVENTIONS DURING FOLLOW-UP BUT WE DIDN'T CONSIDER FOLLOW-UP OR PROGNOSITC DATA FOR THE PRESENT STUDY.

3. Number of patients in HCm group and control group mentioned in abstract only not in the text. Also number of patients in each subgroup of HCM mentioned in the table but not inside the text.

**ANSWER:**THE PATIENTS CONSIDERED WERE 383 (PAG 4), WHILE THE CONTROLS WERE 100 (PAG 5). THE NUMBER OF THE 5 SUBGROUPS IS MENTIONED IN THE TEXT AT PAG 7 (General features of patients divided by morphology).

4. Grading of diastolic dysfunction was not considered for comparison. It was better to classify patients according to the grades of diastolic dysfunction, then compare the subgroup of HCM based on this grades.

**ANSWER:** THANKS TO THE REVIEWER FOR THE COMMENT. THIS COULD BE AN INTERESTING IDEA, BUT ACTUALLY OUR MAIN AIM WAS TO COMPARE THE PREVALENCE OF DIASTOLIC DYSFUNCTION (ACCORDING TO VARIOUS PARAMETERS) IN THE SUBGROUPS CHARACTERIZED BY DIFFERENT MORPHOLOGY. WE BELIEVE THAT IN LITERATURE THERE IS A "GAP" IN THE UNDERSTANDING OF THIS ISSUE.
5. By PWD, the mean of E velocity, A velocity, E/A ratio will not reflect any thing either in HCM patients or controls due to the changes occur from grade of diastolic dysfunction to another

**ANSWER:** WE AGREE WITH THE REVIEWER COMMENT. THE MOST IMPORTANT VARIABLES ARE E/A RATIO > 2 AND DEC TIME. WE INCLUDED EVERYTHING TO BE MORE COMPREHENSIVE. FOLLOWING THE REVIEWER SUGGESTION WE ADDED ON THE TABLE THE E/A RATIO > 2.

6. Significant LVOT gradient was detected in apical HCM. Do you have any explnation because the thickness only involve the apex not the septum.

**ANSWER:** WE THANK THE REVIEWER FOR THE COMMENT. OUR MISTAKE WAS TO WRITE LVOT GRADIENT, WHILE IN APICAL HCM THE GRADIENT WAS MID-VENTRICULAR. WE CORRECTED THE TEXT (SEE THE FIRST PARAGRAPH OF RESULTS) AND THE TABLE.

7. One of the study limitation is calculation of LV mass because the MRI data was not available to all patient. If you have data for a considerable number of patients you can include and correlate with the severity of dystolic dysfunction.

**ANSWER:** UNFORTUNATELY WE DON'T HAVE ENOUGH DATA ON CARDIAC MRI. THE CARDIAC MRI HAS BEEN DONE SOME TIMES YEARS AFTER THE ECHOCARDIOGRAM, WHILE TO DO A GOOD ANALYSIS ON THAT WE WOULD HAVE NEEDED CARDIAC MRI DONE VERY CLOSE TO THE ECHOCARDIOGRAM (AND UNFORTUNATELY THE DATA ARE LACKING)

8. RV dysfunction was detected in 31 HCM patients. Do you have any explanation especially with normal or supernormal LV systolic function?. What is the parameter you relied on for the diagnosis of RV dysfunction?. RVFAC was normal in both HCM and control groups

**ANSWER:** WE THANK THE REVIEWER FOR THE COMMENT. THERE WAS AN ERROR IN TABLE 1 THAT WE CORRECT. THE PATIENT WITH RV DYSFUNCTION WERE 17 (NOT 31 AS PREVIOUSLY REPORTED). AS STATED IN METHODS WE CDEFINED RV SYSTOLIC DYSFUNCTION IN PRESENCE OF EITHER RVFAC LESS THAN 35% OR TAPSE LESS THAN 16 MM. THE AVERAGE RVFA C WAS NORMAL, BUT THERE WERE SOME PATIENTS WITH ABNORMAL RVFAC AND SOME PATIENTS WITH NORMAL RVFAC AND ABNORMAL TAPSE.

9. TAPSe was mentioned in the last paragraph of introduction. Nothing about it in the result section.

**ANSWER:** WE CORRECTED THE TABLE ACCORDING TO THE REVIEWER SUGGESTION.

10. RA volume was inserted for comparison in table 2. It was not mentioned as a method and also in result section

**ANSWER:** WE CORRECTED THE TEXT ACCORDING TO THE REVIEWER SUGGESTION (SEE METHOD SECTION). WE DIDN’T ADD IT IN THE RESULT SECTION BECAUSE THE DIFFERENCE WAS NOT SIGNIFICANT, BUT IF THE REVIEWER FEELS THAT THIS DETAIL SHOULD BE MENTIONED IN THE TEXT WE CAN ADD IT.

11. It was better to describe LA function (passive and active) rather than to describe LAV index

**ANSWER:** WE THANK THE REVIEWER FOR THE COMMENT. ACTUALLY WE BELIEVE THAT LA SIZE IS A PARAMETER THAT HAS MORE RECOGNIZED VALUE, ESPECIALLY IN HCM. WE ARE ACTUALLY WORKING ON ANOTHER PROJECT ON LA FUNCTION.

Reviewer: 2

To reach final conclusions, authors must take another considerations (comments for authors described below) into account.
To investigate the relationship between morphology and left ventricular diastolic dysfunction in patients with hypertrophic cardiomyopathy (HCM), the authors have evaluated LV diastolic function in HCM patients (n=383) with various morphological patterns and normal subjects by using echocardiography. They found that LV diastolic dysfunction in HCM is equally present irrespective of different pattern of hypertrophy. They also demonstrated that LV diastolic dysfunction in HCM is significantly associated with LV outflow obstruction, age, degree of mitral regurgitation (MR) and intraventricular septal thickness (IVS).

This is an interesting and well written paper. However, the authors should address issues described below:

In this study authors measured mitral valve inflow velocity (E and A wave velocity) and peak myocardial early diastolic velocity at the lateral mitral annulus (lateral E’ wave velocity) for evaluation of LV diastolic dysfunction. However, it is well known that E and A wave velocity, as well as E’ velocity and thus E/E’ ratio, are affected by ventricular loading condition such as preload, although TDI velocities are less influenced by loading conditions. In addition, both E and E’ velocity are also increased in patients with moderate to severe mitral regurgitation, which may be associated with increased preload. Indeed, LV outflow obstruction in HCM is usually accompanied by some degree of mitral regurgitation. Therefore, all of the presence of mitral regurgitation (n=134), moderate to severe mitral regurgitation (n=24) and usage of diuretics (n=50) might modify mitral valve inflow velocity and peak myocardial early diastolic velocity. To exclude these possibilities, authors should also investigate diastolic function in HCM patients without LV outflow obstruction (>30mmHg), moderate to severe mitral regurgitation or diuretics usage for the purpose of this study.

ANSWER: WE AGREE WITH THE REVIEWER. THE METHODS WE USUALLY USE FOR DIASTOLIC ASSESSMENT ARE NOT PERFECT AND ARE INFLUENCED BY LOADING CONDITIONS. THE STUDY REFLECTS A "REAL WORLD" EXPERIENCE AND WE TRIED TO EVALUATE ALL THE DIFFERENT METHODS TO ASSESS DIASTOLIC DYSFUNCTION BY ECHOCARDIOGRAPHY. ON THE OTHER SIDE WE HAVE TO UNDERSCORE THAT SIGNIFICANT MITRAL REGURGITANT WAS PRESENT IN A SMALL PERCENTAGE OF THE PATIENTS AND THE USE OF DIURETICS AS WELL WAS IN 13% OF THE WHOLE POPULATION (AND WAS IN THE MAJORITY LOW DOSE THIAZIDIC DIURETIC RATHER THAN LOOP DIURETICS). WE BELIEVE THAT MILD MITRAL REGURGITATION (THAT WAS PRESENT IN LESS THAN HALF OF THE COHORT) DOESN’T AFFECT SIGNIFICANTLY DIASTOLIC ASSESSMENT BY TRANSMITRAL PW, E’ AND E/E’.

IN CONCLUSION WE GENERALLY AGREE WITH THE REVIEWER COMMENT, BUT THIS STUDY REFLECTS A REAL WORLD SITUATION (WITH ALSO REAL LIMITATIONS OF ECHOCARDIOGRAPHY) AND TO EXCLUDE PATIENTS WITH SIGNIFICANT MR OR LV OBSTRUCTION WOULD HAVE AFFECTED THE RELIABILITY OF THE STUDY, CONSIDERING THAT WE ARE DEALING WITH HCM (DISEASE CHARACTERIZED BY THESE FEATURES). WE ADDED A PARAGRAPH IN THE LIMITATIONS ABOUT IT.

Reviewer: 3

1. The authors should identify how many HCM patients were in the database from 1999 to 2011, and how many were screened and excluded for each/every exclusion criterion to give readers an idea of the generalizability of the data.

ANSWER: WE MODIFIED THE TEXT ACCORDING TO THE REVIEWER SUGGESTION (SEE METHOD SECTION, PAG 4)

2. What was the rationale for including a control population? Would not each morphological HCM type serve as a comparator to the other?

ANSWER: THE RATIONAL OF INCLUDING A SEX AND AGE MATCHED CONTROL POPULATION
WAS TO COMPARE ALL THE VARIOUS SUBGROUP WITH A NORMAL COHORT. ONE OF OUR AIM WAS TO SAY THAT DIASTOLIC FUNCTION WAS IMPAIRED IN ALL SUBTYPES OF HCM, DESPITE THE PRESENCE OF A DIFFERENT DISTRIBUTION OF HYPERTROPHY. TO REACH THIS PURPOSE WE HAD TO HAVE A NORMAL COUNTERPART.

3. The authors should provide an actual echocardiographic 2D image of each morphological HCM type described on page 5, paragraph 4.
ANSWER: DONE

4. 2D and m-mode measurements and cut-off values for LV hypertrophy, as detailed in the ASE 2005 Chamber Quantification Guidelines, have different cut-off values. Can the authors show, perhaps in table, how these different values were handled and how they were applied to the study population?
ANSWER: IF THE QUESTION REFERS TO THE DIAGNOSIS, WE GENERALLY CONSIDERED THE CUTOFF VALUE OF 15 MM WHICH WAS FOUND IN THE MAJORITY OF THE PATIENTS IN BOTH M-MODE AND 2D. OF COURSE THE PATIENTS WITH AHCM HAD BOTH THE PRESENCE OF A SUGGESTIVE ECG AND 2D ECHO HYPERTROPHY AT THE APEX. THERE WERE ALSO PATIENTS WITH ABNORMAL ECG (SUGGESTIVE OF HCM) AND HYPERTROPHY AT 2D AND M-MODE BETWEEN 13 AND 15 MM.
IF THE REVIEWER BELIEVE THAT THIS SPECIFICATION IS NEEDED WE CAN ADD IT IN THE TEXT.

5. Why was only lateral e' measured?
ANSWER: IN OUR LAB WE RELY ON LATERAL E’ FOR EVALUATION OF TDI IN HCM.
ALTHOUGH THIS HAS NOT BEEN DEMONSTRATED IN A STUDY COMPARING CATH AND ECHO WE BELIEVE THAT THE PRESENCE OF HYPERTROPHY THAT USUALLY INVOLVES THE SEPTUM (IN REVERSE, SIGMOID AND SYMMETRIC WHERE BOTH THE POSTERIOR WALL AND THE SEPTUM ARE THICKENED) COULD AFFECT A CORRECT EVALUATION OF LONGITUDINAL FUNCTION AND RELAXATION.

6. The Results section has too many numbers and is difficult to read (especially with OR data). In general, detailed numbers can be presented in tables and figures and the Results section should not repeated these data but provide overall findings and trends while referring to tables and figures.
ANSWER: WE THANK THE REVIEWER FOR THE COMMENT. WE REDUCED A LOT THE RESULT SECTION REFERRING TO TABLES AND FIGURES.

7. Do the authors have any clinical data (development of clinical HF, hospitalization for HF, incidence of AF, VT, death) that they could correlate with the diastolic variables/morphological HCM type?
ANSWER: UNFORTUNATELY THE DATA ON FOLLOW-UP WERE NOT COMPLETE. ACTUALLY OUR STUDY WAS FOCUSED ON THE UNDERSTANDING OF DIASTOLIC FUNCTION AND RELATIONSHIP WITH MORPHOLOGY IN HCM PATIENTS.

8. Are any BNP or NT-proBNP data available to correlate with the diastolic indices?
ANSWER: BNP SAMPLES WERE NOT COLLECTED, UNLESS THERE WAS A CLINICAL REASON. THUS DATA ARE NOT COMPLETE.

9. Are any invasive hemodynamic data available to corroborate the diastolic findings in this study?
ANSWER: NO, THERE ARE NOT INVASIVE HEMODYNAMIC DATA. PATIENTS WERE STUDIED WITH INVASIVE HEMODYNAMIC ONLY IF THERE WERE SOME CLINICAL INDICATIONS TO JUSTIFY IT.

10. More detail, analysis and discussion of the relation of diastolic function and genetic markers is
warranted.

ANSWER: WE AGREE WITH THE REVIEWER COMMENT AND WE MODIFIED THE TEXT ACCORDINGLY. SEE THE LAST PARAGRAPH OF DISCUSSION.
11. The Limitations section can be expanded to cover some of the issues raised above. ANSWER: WE THANK THE REVIEWER FOR THE COMMENT. WE EXPANDED THE LIMITATIONS ACCORDINGLY.

**VERSION 2 – REVIEW**

| REVIEWER         | Ashraf M Anwar |
|------------------|----------------|
| CARDIOLOGY DEP, KAFH JEDDAH, SAUDI ARABIA |

| REVIEW RETURNED | 23-Apr-2014 |

| GENERAL COMMENTS | The study included good number of pts with HCM. The aim was to describe diastolic dysfunction in different HCM subtypes. 1. As a tertiary center, most of the included patients are regularly followed. The echo parameters need to be correlated with the duration of medical ttt. For example these parameters may show difference between HCM pt recently diagnosed and not on maximum ttt and other pt with long standing ttt. 2. Serial echo parameters will be of great benefit for comparison especially in pts with restrictive pattern and moderate to severe MR. 3. RV dysfunction (systolic and diastolic) in HCM patient may not be related to LV dysfunction. So, a comparison between HCM and control group will be an addition. |

| REVIEWER         | Tetsu Yamakado, MD |
|------------------|---------------------|
| DEPARTMENT OF CARDIOLOGY |
| OKANAMI GENERAL HOSPITAL |

| REVIEW RETURNED | 19-Apr-2014 |

| GENERAL COMMENTS | Some weeks ago, I reviewed the first edition of this paper. I wrote my comment described below. But authors seem not to respond comments in the revised paper. "To investigate the relationship between morphology and left ventricular diastolic dysfunction in patients with hypertrophic cardiomyopathy (HCM), the authors have evaluated LV diastolic function in HCM patients (n=383) with various morphological patterns and normal subjects by using echocardiography. They found that LV diastolic dysfunction in HCM is equally present in different pattern of hypertrophy. They also demonstrated that LV diastolic dysfunction in HCM is significantly associated with LV outflow obstruction, age, degree of mitral regurgitation (MR) and intraventricular septal thickness (IVS). This is an interesting and well written paper. However, the authors should address issues described below; In this study authors measured mitral valve inflow velocity (E and A wave velocity) and peak myocardial early diastolic velocity at the lateral mitral annulus (lateral E' wave velocity) for evaluation of LV diastolic dysfunction. However, it is well known that E and A wave velocity, as well as E' velocity and thus E'/E ratio, are affected by ventricular loading condition such as preload, although TDI velocities are less influenced by loading conditions. In addition, both E and E' velocity are also increased in patients with moderate to severe mitral |


regurgitation, which may be associated with increased preload. Indeed, LV outflow obstruction in HCM is usually accompanied by some degree of mitral regurgitation. Therefore, all of the presence of mitral regurgitation (n=134), moderate to severe mitral regurgitation (n=24) and usage of diuretics (n=50) might modify mitral valve inflow velocity and peak myocardial early diastolic velocity. To exclude these possibilities, authors should also investigate diastolic function in HCM patients without LV outflow obstruction (>30mmHg), moderate to severe mitral regurgitation or diuretics usage for the purpose of this study."

REVIEWER
Hisham Dokainish
McMaster University

REVIEW RETURNED
03-Apr-2014

- The reviewer completed the checklist but made no further comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3
Reviewer Name: Hisham Dokainish
Institution and Country: McMaster University

Please state any competing interests or state 'None declared': None declared
If you have any further comments for the authors please enter them below.

Prior comments have been addressed.

Reviewer: 2
Reviewer Name: Tetsu Yamakado, MD
Institution and Country: Department of Cardiology
Okanami General Hospital

Please state any competing interests or state 'None declared': None declared

Some weeks ago, I reviewed the first edition of this paper. I wrote my comment described below. But authors seem not to respond comments in the revised paper.

"To investigate the relationship between morphology and left ventricular diastolic dysfunction in patients with hypertrophic cardiomyopathy (HCM), the authors have evaluated LV diastolic function in HCM patients (n=383) with various morphological patterns and normal subjects by using echocardiography. They found that LV diastolic dysfunction in HCM is equally present different pattern of hypertrophy. They also demonstrated that LV diastolic dysfunction in HCM is significantly associated with LV outflow obstruction, age, degree of mitral regurgitation (MR) and intraventricular septal thickness (IVS).

This is an interesting and well written paper. However, the authors should address issues described below:

In this study authors measured mitral valve inflow velocity (E and A wave velocity) and peak myocardial early diastolic velocity at the lateral mitral annulus (lateral E’ wave velocity) for evaluation of LV diastolic dysfunction. However, it is well known that E and A wave velocity, as well as E’ velocity and thus E’/E ratio, are affected by ventricular loading condition such as preload, although TDI velocities are less influenced by loading conditions. In addition, both E and E’ velocity are also increased in patients with moderate to severe mitral regurgitation, which may be associated with increased preload. Indeed, LV outflow obstruction in HCM is usually accompanied by some degree of
mitral regurgitation. Therefore, all of the presence of mitral regurgitation (n=134), moderate to severe mitral regurgitation (n=24) and usage of diuretics (n=50) might modify mitral valve inflow velocity and peak myocardial early diastolic velocity. To exclude these possibilities, authors should also investigate diastolic function in HCM patients without LV outflow obstruction (>30mmHg), moderate to severe mitral regurgitation or diuretics usage for the purpose of this study.

WE THANK THE REVIEWER FOR HIS COMMENT. WE TRY TO ANSWER EACH POINT. THE REVIEWER STATED THAT E AND A WAVE VELOCITY AT TRANSMITRAL DOPPLER AS WELL AS E'/E RATIO ARE AFFECTED BY VENTRICULAR LOADING CONDITIONS. GENERALLY WE AGREE WITH THIS COMMENT, BUT WE BELIEVE THIS IS THE BEST WAY TO EVALUATE DIASTOLIC FUNCTION BY ECHOCARDIOGRAPHY. WE ADDED A SENTENCE IN THE LIMITATION, CONCERNING THIS POINT.

ON THE OTHER SIDE WE BELIEVE THAT A MILD (OR EVEN A TRIVIAL) MR WOULD NOT AFFECT SIGNIFICANTLY THE ASSESSMENT OF DIASTOLIC FUNCTION USING DOPPLER AND TDI AND THE PATIENTS WITH MODERATE TO SEVERE MR WERE A MINORITY (ONLY 6%). DIURETICS WERE USED ONLY IN THE 13% OF THE WHOLE POPULATION (AND IN THE MAJORITY LOW DOSE THIAZIDIC DIURETIC RATHER THAN LOOP DIURETICS, IN THE MAJORITY), SO AGAIN WE DON'T THINK THAT THERE IS A SIGNIFICANT IMPACT ON DOPPLER MEASUREMENTS. WE MENTIONED THE USE OF DIURETICS IN THE LIMITATION SECTION.

WE BELIEVE THAT EXCLUDING PATIENTS WITH LV OBSTRUCTION AND WITH MITRAL VALVE DISEASE WOULD GENERATE A STUDY THAT DOESN'T MIRROR THE DISEASE FEATURES IN THE REAL WORLD, BEING POTENTIALLY MISLEADING. IN PARTICULAR THE ANALYSIS OF LV OBSTRUCTION ROLE IN DIASTOLIC DYSFUNCTION IS SOMETHING THAT WE BELIEVE MAY BE USEFUL TO BETTER UNDERSTAND HOW ARCHITECTURAL CHANGES AFFECT RELAXATION AND FILLING IN THIS DISEASE.

AS THE REVIEWER WROTE IT IS IN SOMEWAY EXPECTED TO FIND A SIGNIFICANT ASSOCIATION BETWEEN SIGNIFICANT MR AND LA ENLARGEMENT AND E/E'RATIO, BUT THIS TYPE OF ANALYSIS ALLOWS US TO SAY THAT THE OTHER PARAMETERS CONSIDERED (AND IN PARTICULAR LV OBSTRUCTION) ARE ASSOCIATED INDEPENDENTLY WITH DIASTOLIC DYSFUNCTION (SEE LIMITATIONS).

Reviewer: 1
Reviewer Name Ashraf M Anwar
Institution and Country Cardiology Dep, KFAFH Jeddah, saudi Arabia
Please state any competing interests or state ‘None declared’: NO

The study included good number of pts with HCM. The aim was to describe diastolic dysfunction in different HCM subtypes.
1. As a tertiary center, most of the included patients are regularly followed. The echo parameters need to be correlated with the duration of medical ttt. for example these parameters may show difference between HCM pt recently diagnosed and not on maximum ttt and other pt with long standing ttt.

UNFORTUNATELY THE DATA ABOUT THE FIRST DIAGNOSIS ARE UNCOMPLETE AND FRAGMENTED. THE MAJORITY OF THE PATIENTS HAVE A RECENT DIAGNOSIS OF HCM (WITHIN 2 YEARS). THE POINT RAISED BY THE REVIEWER IS DEFINETELY INTERESTING, BUT IT WOULD BE DIFFICULT TO DEMONSTRATE ANY ROLE OF MEDICAL THERAPY ON DIASTOLIC FUNCTION IN A STUDY THAT IS ONLY RETROSPECTIVE AND NON-RANDOMIZED.

2. Serial echo parameters will be of great benefit for comparison especially in pts with restrictive
pattern and moderate to severe MR.

WE THANK THE REVIEWER FOR THE COMMENT. WE AGREE THAT THIS WOULD BE REALLY INTERESTING, BUT UNFORTUNATELY WE DON'T HAVE SERIAL PARAMETERS IN ENOUGH PATIENTS. BEING STANFORD A REFERRAL CENTER FOR CARDIOMYOPATHIES QUITE A LOT OF PATIENTS HAVE BEEN REFERRED FOR A SECOND OPINION AND THEN RE-REFERRED TO THE ORIGINAL CENTER. THE POINT IS UNDERSCORED IN THE LAST PART OF THE LIMITATIONS.

3. RV dysfunction (systolic and diastolic) in HCM patient may not be related to LV dysfunction So, a comparison between HCM and control group will be an addition.

WE COMPARED HCM AND CONTROLS FOR RV DYSFUNCTION (TABLE 2). WE DISCUSSED EXTENSIVELY THE TOPIC IN OUR RECENT PAPER PUBLISHED ON AJC.