

中国医学科学院阜外医院

FUWAI Hospital, CAMS & PUMC



Sex Differences in Hypertrophic Obstructive Cardiomyopathy

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1

Introduction

2

Methods

3

Results

4

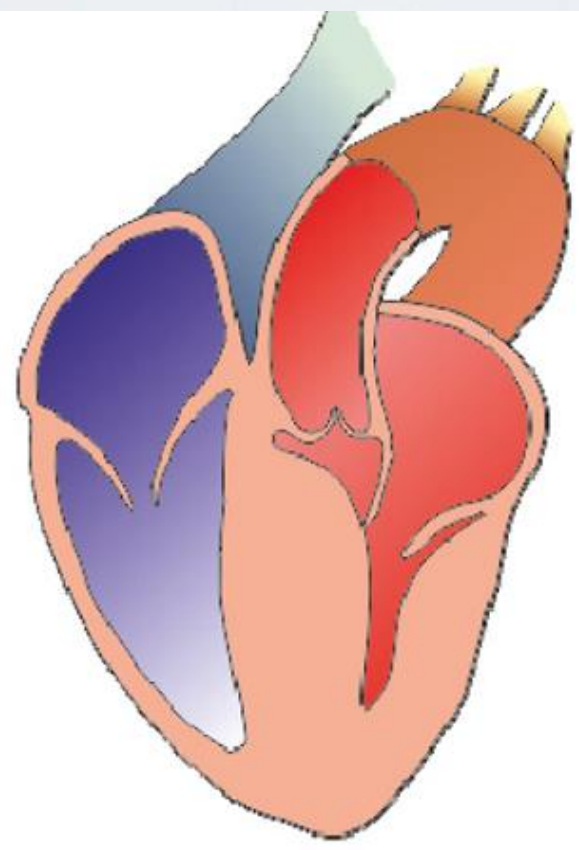
Discussion



Introduction

□ Hypertrophic cardiomyopathy (HCM)

- An inheritable disease with asymmetric ventricular wall thickening and often involving ventricular septum
- with a prevalence of 1/500
- characterized by different degrees of diastolic dysfunction
- The phenotypic spectrum is heterogeneous.





Introduction

□ Sex is known to impact many cardiovascular diseases

- heart failure
- valvular heart disease
- coronary artery disease
- dilated cardiomyopathy

Sex differences in HCM are less well understood



Introduction

□ β 1 adrenergic receptor autoantibody (β 1-AAb)

- One of the cardiac GPCR-AABs
- binding with the second extracellular ring of β 1 receptors
- agonist like effect, promoting cardiac contractility, heart rate and cardiac output
- existing in kinds of cardiomyopathies
- Antibody titers correlate with the severity of heart failure

□ M2 muscarinic receptor autoantibody (M2-AAb)

- One of the cardiac GPCR-AABs
- binding with the second extracellular ring of M2 receptors
- agonist like effect, decreasing cardiac contractility, heart rate and cardiac output
- existing in kinds of cardiomyopathies
- Antibody titers correlate with the severity of heart failure



Introduction

□ Previous research of our group showed:

- HCM patients had significantly higher concentrations of $\beta 1$ -AAb and M2-AAb than normal controls (NC). ▶
- HCM patients with left atrial diameter ≥ 50 mm or moderate-severe mitral regurgitation had significantly higher concentrations of $\beta 1$ -AAb and M2-AAb.
- In HOCM patients, the two autoantibodies were positively correlated with resting left ventricular outflow tract gradient (LVOTG), and $\beta 1$ -AAb correlated to the maximum ventricular thickness.

- *The relationship between $\beta 1$ adrenergic, M2 muscarinic receptor autoantibody and hypertrophic cardiomyopathy. Exp Physiol. 2019 Dec. PMID: 31808213.*





Table 1 Comparison of serum β 1-AAb concentrations in patients with various types of HCM

group	β 1 -AAb (ng/ml)	P1	P2	P3
HCM (<i>n</i> =134)	48.23 (38.49-55.98)	<0.001		
HOCM (<i>n</i> =73)	47.14 (38.17-57.26)	<0.001	0.748	0.609
LHOCM (<i>n</i> =22)	47.43 ± 15.82	<0.001	0.631	
NOCM (<i>n</i> =39)	50.23 (39.30-54.91)	<0.001		
NC (<i>n</i> =40)	24.51 ± 6.89			

P1 for comparison between each HCM subgroup and NC group respectively; P2 for comparison between HOCM or LHOCM group and NOCM group; P3 for comparison between HOCM and LHOCM patients;



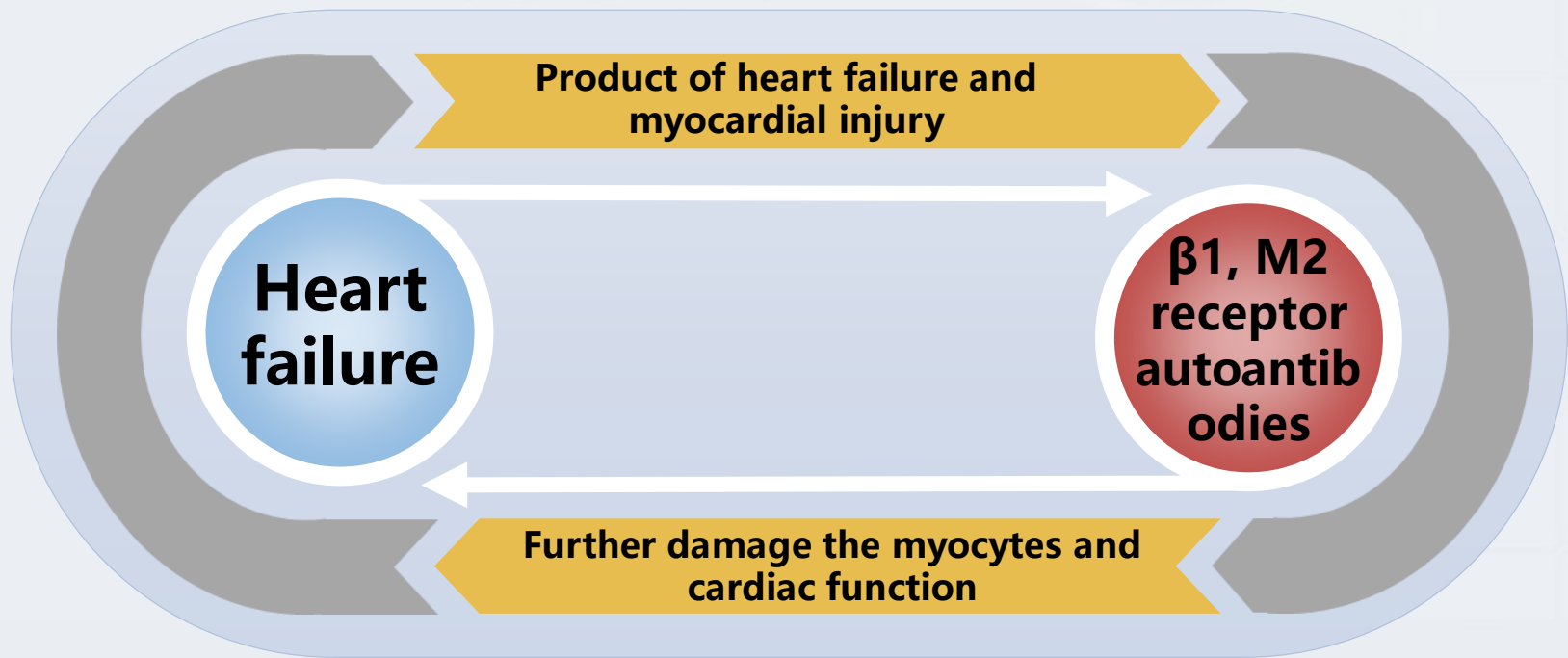
Table 2 Comparison of serum M2-AAb concentrations in patients with various types of HCM

group	M2-AAb(ng/ml)	P1	P2	P3
HCM (n=134)	22.90 (17.23-29.56)	<0.001		
HOCM (n=73)	23.70 (18.07-31.80)	<0.001	0.167	0.302
LHOCM (n=22)	22.93±8.21	0.002	0.869	
NOCM (n=39)	23.04±9.61	0.002		
NC (n=40)	17.14±5.66			

P1 for comparison between each HCM subgroup and NC group respectively; P2 for comparison between HOCM or LHOCM group and NOCM group; P3 for comparison between HOCM and LHOCM patients;



Introduction





Introduction

- This study was to investigate sex differences in HOCM patients from two aspects:
 - Clinical characteristics
 - Concentrations of β 1-AAb and M2-AAb



1

Introduction

2

Methods

3

Results

4

Discussion



Methods

□ Group

- HOCM group: 73 HOCM patients (33 women and 40 men) were consecutively recruited in Fuwai Hospital
- NC group: 40 healthy subjects (18 women and 22 men) without cardiac or autoimmune diseases
- HOCM patients were divided into two groups according to their sex, and the sex differences were compared.



Methods

□ Diagnosis of HOCM

- maximal left ventricular (LV) wall thickness ≥ 15 mm measured by echocardiography or CMR
- LVOTG ≥ 30 mmHg at rest
- absence of other cardiac or systemic diseases leading to myohypertrophy



Methods

□ Exclusion criteria

- history of alcohol septal ablation, septal myectomy, permanent mechanical device implantation
- significant changes in structure and function of the heart
- history of severe liver and kidney diseases, autoimmune diseases, malignant tumors
- trauma, or surgery within 6 months prior to the study
- acute, chronic infectious disease or recovery from acute infection
- glucocorticoid or immunosuppressant use



Methods

□ Clinical Evaluation

HOCM

**medical history,
physical
examination**

**transthoracic
echocardiography
、CMR**

**12-lead
electrocardiogra
phy、Holter**

**routine
hematology tests**



Methods

□ Sample analysis

HOCM group and
NC group

No use or
discontinuation of β -
blocker 3 days
before blood
collection

Fasting peripheral
venous serum,
centrifugation

Quantitative detection of
 β 1-AAb/ M2-AAb by
ELISA kit

Each sample was
tested simultaneously
in two wells, the
average value was the
final result



1

Introduction

2

Methods

3

Results

4

Discussion



Result (1)

Table 1 Comparison of serum autoantibody concentrations in HOCM patients and normal controls

variable	HOCM (n=73)	NC (n=40)	P-value
β 1-AAb (ng/ml)	47.14 (38.17-57.26)	24.51 \pm 6.89	<0.001
M2-AAb (ng/ml)	23.70 (18.07-31.80)	17.14 \pm 5.66	<0.001

HOCM patients had significantly higher concentrations of β 1-AAb and M2-AAb than NC.

Table 2 Comparison of clinical characteristics in HOCM patients of different genders

variable	Women(n=33)	Men(n=40)	P-value
Age (years)	52.91±15.66	47.18±12.37	0.085
Body mass index (kg/m ²)	26.04±3.69	26.94±3.26	0.277
Heart rate (beats/min)	72.36±12.82	71.47±11.37	0.755
NYHA functional class III or IV	22(66.7)	20(50.0)	0.152
Chest pain	30(90.9)	39(97.5)	0.218
Palpitation	10(30.3)	10(25.0)	0.613
Syncope	6(18.2)	8(20.0)	0.844
Family history of SCD	3(9.1%)	3(7.5%)	0.805
Family history of HCM	3(9.1%)	11(27.5%)	0.047
Hypertension	13(39.4%)	11(27.5%)	0.282
Diabetes mellitus	4(12.1%)	5(12.5%)	0.961
Hypercholesterolemia	9(27.3%)	18(45.0)	0.118
Echocardiography			
Septal wall thickness (mm)	20.00±3.90	22.38±5.14	0.032
Left atrium diameter (mm)	39.7±5.85	43.7±6.20	0.006
Left ventricular diameter (mm)	40.82±5.07	43.45±4.05	0.016
Left ventricular ejection fraction (%)	67.76±3.76	68.78±3.70	0.249
SAM	26(78.8)	40(100.0%)	0.002

Table 2 Comparison of clinical characteristics in HOCM patients of different genders

variable	Women(n=33)	Men(n=40)	P-value
Atrial fibrillation*	3(9.7)	5(13.5)	0.625
Atrial tachycardia*	14(45.2)	11(29.7)	0.189
Non-sustained VT*	6(19.4)	5(13.5)	0.515
Maximum wall thickness \geq 30mm	4(13.8)	9(25.7)	0.238
Moderate or severe mitral regurgitation	18(54.5)	21(52.5)	0.862
Combined with mid-ventricular obstruction	5(15.2)	5(12.5)	0.743
Left atrium diameter \geq 50 mm	4(13.8%)	11(31.4%)	0.097
LVOTG	92.06 \pm 32.49	84.48 \pm 26.78	0.123
NT-proBNP	1199.00(585.60-2504.00)	707.35(344.15-1374.25)	0.044



Result (2)

□ In HOCM patients, males had

- larger left heart diameter,
- thicker ventricular septum,
- higher proportion of SAM phenomenon,
- higher proportion of HCM family history

□ In HOCM patients, females had

- higher concentrations of NT-proBNP

□ Possible trends for female HOCM patients

- presented at older age
- demonstrated higher LVOTG

Table 3 Comparison of β 1-AAb and M2-AAb between HOCM patients of different genders

variable	Women(n=33)	Men(n=40)	P-value
β 1-AAb (ng/ml)	43.47 (34.81-64.12)	49.21 (40.84-54.75)	0.731
M2-AAb (ng/ml)	26.20 (18.13-39.10)	22.83 (17.23-28.63)	0.101

Table 4 Correlation between log β 1-AAb levels and clinical characteristics in HOCM patients of different genders

variable	Women			Men		
	value	r	P -value	value	r	P -value
Age (years)	52.91±15.66	0.002	0.989	47.18±12.37	0.122	0.453
Body mass index (kg/m ²)	26.04±3.69	0.132	0.464	26.94±3.26	-0.008	0.962
Heart rate (beats/min)	72.36±12.82	-0.220	0.281	71.47±11.37	0.201	0.214
LVOTG at rest (mmHg)	92.06±32.49	0.353	0.044	84.48±26.78	0.140	0.388
Laboratory test						
NT-proBNP (pmol/L)	1199.00(585.60-2504.00)	-0.069	0.711	707.35(344.15-1374.25)	0.243	0.141
Cardiac troponin I (ng/ml)	0.01 (0.01-0.03)	-0.151	0.418	0.02 (0.00-0.06)	-0.042	0.813
hs-CRP (mg/L)	1.10 (0.70-2.01)	0.065	0.725	1.37 (0.73-1.84)	0.122	0.484

Table 4 Correlation between log β 1-AAb levels and clinical characteristics in HOCM patients of different genders

variable	Women (n=29)			Men (n=35)		
	value	r	P -value	value	r	P -value
Cardiovascular magnetic resonance						
Left atrium diameter (mm)	39.16±8.98	0.349	0.064	44.11±9.16	0.072	0.681
Left ventricular end-diastolic diameter (mm)	43.82±3.96	0.276	0.148	48.23±4.29	0.021	0.905
Maximum wall thickness (mm)	22.00 (19.00-24.50)	0.289	0.128	24.00 (22.00-30.00)	0.181	0.299
Left ventricular ejection fraction (%)	67.08±5.95	0.269	0.644	63.63±9.10	0.008	0.962
Left ventricular end-diastolic volume index (ml/m ²)	73.56±16.35	0.015	0.939	78.90±15.56	0.074	0.672
Left ventricular end-systolic volume index (ml/m ²)	23.43±4.86	0.406	0.029	29.12±11.87	0.031	0.859
Stroke volume index index (ml/m ²)	49.34±11.63	0.024	0.902	49.83±9.93	0.031	0.859
Left ventricular mass (g/m ²)	66.74±20.12	0.212	0.269	90.33±32.83	0.113	0.517
Cardiac index [L/(min·m ²)]	3.43±0.85	0.186	0.335	3.43±0.82	0.067	0.701
Septal wall thickness (mm)	22.00 (19.00-24.50)	0.289	0.128	24.00 (22.00-30.00)	0.181	0.299

Table 5 Correlation between logM2-AAb levels and clinical characteristics in HOCM patients of different genders

variable	Women			Men		
	value	r	P -value	value	r	P -value
Age (years)	52.91±15.66	-0.002	0.992	47.18±12.37	0.018	0.911
Body mass index (kg/m ²)	26.04±3.69	-0.117	0.515	26.94±3.26	0.068	0.675
Heart rate (beats/min)	72.36±12.82	-0.050	0.781	71.47±11.37	0.007	0.967
LVOTG at rest (mmHg)	92.06±32.49	0.279	0.116	84.48±26.78	0.106	0.514
Laboratory test						
NT-proBNP (pmol/L)	1199.00(585.6 0-2504.00)	-0.019	0.918	707.35(344.15 -1374.25)	0.290	0.077
Cardiac troponin I (ng/ml)	0.01 (0.01- 0.03)	-0.183	0.324	0.02 (0.00- 0.06)	-0.100	0.573
hs-CRP (mg/L)	1.10 (0.70- 2.01)	-0.038	0.838	1.37 (0.73- 1.84)	-0.109	0.533

Table 5 Correlation between logM2-AAb levels and clinical characteristics in HOCM patients of different genders

variable	Women (n=29)			Men (n=35)		
	value	r	P - value	value	r	P -value
Cardiovascular magnetic resonance						
Left atrium diameter (mm)	39.16±8.98	0.365	0.051	44.11±9.16	0.078	0.657
Left ventricular end-diastolic diameter (mm)	43.82±3.96	0.217	0.259	48.23±4.29	0.026	0.884
Maximum wall thickness (mm)	22.00 (19.00-24.50)	0.278	0.144	24.00 (22.00-30.00)	0.186	0.284
Left ventricular ejection fraction (%)	67.08±5.95	-0.090	0.644	63.63±9.10	0.073	0.676
Left ventricular end-diastolic volume index (ml/m ²)	73.56±16.35	0.243	0.204	78.90±15.56	-0.132	0.451
Left ventricular end-systolic volume index (ml/m ²)	23.43±4.86	0.393	0.035	29.12±11.87	-0.122	0.485
Stroke volume index index (ml/m ²)	49.34±11.63	0.205	0.287	49.83±9.93	-0.058	0.739
Left ventricular mass (g/m ²)	66.74±20.12	-0.257	0.178	90.33±32.83	0.113	0.517
Cardiac index [L/(min·m ²)]	3.43±0.85	0.054	0.782	3.43±0.82	-0.100	0.569
Septal wall thickness (mm)	22.00 (19.00-24.50)	0.278	0.144	24.00 (22.00-30.00)	0.186	0.284



Result (3)

- Concerning the concentrations of β 1-AAb and M2-AAb, there was no significant sex difference in HOCM patients .
- In female HOCM patients, β 1-AAb significantly correlated to left ventricular end-systolic volume index.
- In male HOCM patients, there was no index significantly correlated to β 1-AAb or M2-AAb.

1

Introduction

2

Methods

3

Results



4

Discussion



Discussion (1)

Previous studies indicated:

- Patients with heart failure had higher titers of β 1-AAb and M2-AAb than NC, regardless of the primary heart disease.
- The titers of the two autoantibodies showed no significant difference between etiological groups, but related to the degree of heart failure.



Discussion (1)

□ HOCM patients have myocardial injury

- reduced density of coronary capillary vessel bed
- imbalance between myocardial oxygen supply & demand
- microvascular dysfunction
- myocardial fibrosis

□ Left ventricular diastolic dysfunction in HOCM patients

- cardiac hypertrophy
- microvascular dysfunction
- decreased compliance of the ventricular wall
- left ventricular outflow obstruction
- arrhythmia

The concentrations of β 1-AAb and M2-AAb in HOCM patients possibly associated with myocardial injury and diastolic dysfunction.



Discussion (2)

- Sex differences exist in clinical characteristics of HOCM patients , such as left heart diameter, thicker ventricular septum, NT-proBNP, LVOTG and etc.
- consistent with previous research results



Discussion (3)

Table 6 Comparison of β 1-AAb and M2-AAb between 134 HCM patients of different genders

variable	Women(n=52)	Men(n=82)	P-value
β 1-AAb (ng/ml)	49.14(37.06, 63.27)	48.19(38.98- 54.07)	0.275
M2-AAb (ng/ml)	26.26(21.48, 36.69)	21.31(15.81, 27.21)	0.001

sex differences in the autoimmune mechanism involved in HCM?



Discussion (4)

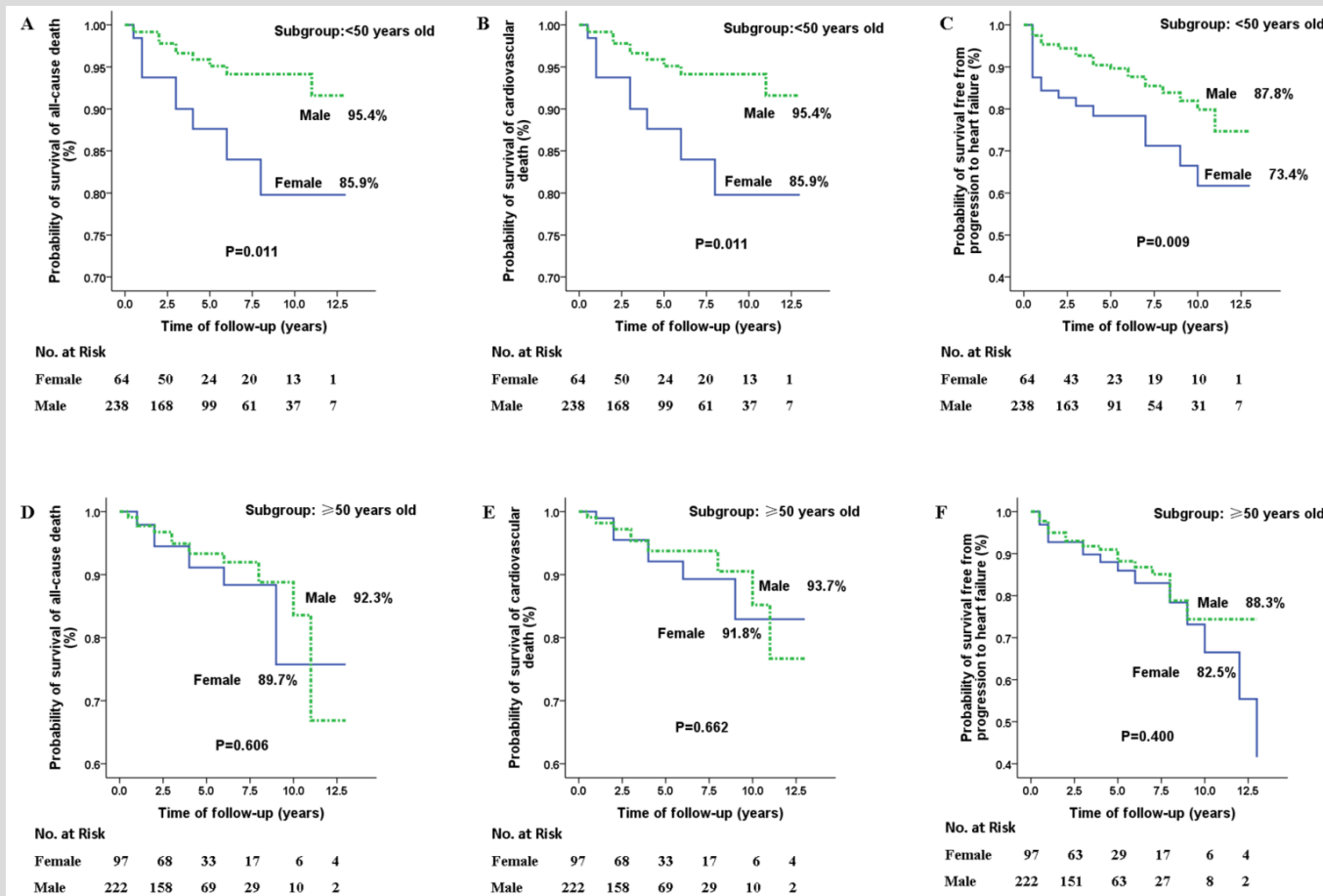
Women with HCM present at more advanced age, more symptoms, worse cardiopulmonary exercise tolerance, and worse survival than men.

- n=3673 HCM patients, 1661 women and 2012 men, during 1975 to 2012
- median follow-up period of 10.9 years

Geske JB, et al. Eur Heart J, 2017

Female sex was an independent risk factor for all-cause mortality, cardiovascular death and chronic heart failure in Chinese HCM patients.

n=621 HCM patients, 161 women and 460 men, during 1999 to 2011
 4 year follow-up period on average (range 2-7 years)
 only in HCM patients <50 years old





Discussion

□ Possible reasons for gender differences

- the expression of genes located on the sex chromosomes
- endocrine differences
- psychosocial factors
- gender differences in autoimmune mechanisms ?

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Thanks!





Introduction

□ cardiac β 1 adrenergic receptor

- sympathetic nerve—catecholamine
- promoting cardiac contractility
- Promoting heart rate and cardiac output

□ cardiac M2 muscarinic receptor

- parasympathetic nerve—acetylcholine
- decreasing cardiac contractility
- decreasing heart rate and cardiac output



Discussion

Geske JB, Ong KC, Siontis KC, et al. Women with hypertrophic cardiomyopathy have worse survival [J]. Eur Heart J, 2017, 38(46): 3434-3440.

Yilu Wang, Jizheng Wang, Yubao Zou, et al. Female sex is associated with worse prognosis in patients with hypertrophic cardiomyopathy in China [J]. PLoS One, 2014, 9(7): e102969.

Female sex was an independent risk factor for all-cause mortality, cardiovascular death and chronic heart failure progression in HCM patients.

There may be gender differences in the autoimmune mechanisms involved in HCM