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Effect of age and sex on echocardiographic left ventricular diastolic function parameters in patients with preserved ejection fraction and normal valvular function

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Abstract

Background: *We conducted a retrospective study to specify the effect of age and gender on echocardiographic left ventricular diastolic function parameters.*

Methods: *We included echocardiograms done in our institution between 1995 and 2007, for which data on diastolic function were available. In order to target a population as close as possible to healthy subjects, echocardiograms reporting abnormal contraction, valvulopathy or extreme data were excluded.*

Results: *A total of 14,298 patients (mean age 58.53 years; men 49.1%) were included in the study. Sex did not influence E/A ratio ($p = 0.298$) but age decreased it significantly ($p < 0.001$). E/e ratio increased significantly with age ($p < 0.001$) and was higher in women than in men ($p < 0.001$). After the age of 40, more than 10% of the patients had an E/e ratio superior than 8.*

Conclusions: *To our knowledge, this is the most imposing study — in terms of number of patients from first to tenth decade of life that were included — addressing the effect of age and gender on diastolic function. Our results stress the need for future prospective trials to establish normal diastolic function parameters according to age and gender, notably for the E/e ratio for which a significant proportion of our population had a ratio superior of what is actually considered normal.* (Cardiol J 2013; 20, 5: 513–518)

Key words: function, left ventricular, diastole, gender, echocardiography, echocardiography, Doppler

Introduction

Even with normal aging process, changes in myocardium occur and may modify lusitropic function of the heart. These changes include a remodeling of the myocardial interstitium, an increase in myocardium collagen content and a prominence of myocardial fibrosis, probably due to the activation of the renin–angiotensin–aldosterone axis [1]. This heart aging phenomenon surely affects the diastolic function of our patients and needs to be readily and easily assessed. In fact, facing the current growing incidence of diastolic heart failure, defining the border between normal aging process

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and pathologic diastolic function become of the utmost importance.

Unfortunately, evaluating cardiac diastolic function non-invasively can be a very tricky task. In fact, myocardial relaxation, left ventricle (LV) stiffness, and filling pressures are complex phenomena that can only be assessed indirectly by echocardiography. It is therefore not surprising that in the last decade, a large number of echocardiography indicators have emerged in an effort to better characterize diastolic function. The most commonly used, because of their ease of acquisition, remain the mitral E/A wave velocities ratio and the mitral E/e ratio. Mitral E-wave velocity reflects early diastole while mitral A-wave reflects late diastole. They vary respectively, according to preload and alterations in LV relaxation for the former and for the latter, LV compliance and left atrium contractile function. The E/A wave velocities ratio can further classify diastolic function as normal, impaired LV relaxation (pseudonormal) and restrictive LV filling. The early diastolic annular velocity (e) is mainly influenced by LV relaxation, and to a lesser extent, by preload, systolic function and LV minimal pressure. This is especially true in situations of impaired relaxation. Therefore, it is possible to estimate the LV filling pressure using the E/e ratio, since e corrects the effect of relaxation on mitral E velocity [2]. However, although these echocardiography parameters have been widely used for many years to assess diastolic function, expected values for an individual of given age and sex remain imprecise. This reflects the fact that the literature to date has focused on a small number of healthy volunteers or sub-groups of older adults [2–4].

We conducted a large retrospective trial to clarify the effect of normal aging and gender on echocardiographic LV diastolic function parameters in a selected population as close as possible to healthy subjects.

Methods

Data collection

We conducted a retrospective study using echocardiogram database including all exams done at the Centre Hospitalier Universitaire de Sherbrooke between 1995 and 2007. The decision to discontinue data revision in 2007 is based on the fact that this is the last year for which all data were available at the time of the study beginning. We used the computerized databank CIRESSS (Centre Informatisé de Recherche Évaluative en Services et Soins de Santé) of our healthcare center to access patients data. We included all the echocardiograms with preserved LV ejection fraction (LVEF > 50% and/or no contraction deficit) and having available evaluation of diastolic function.

We excluded all the exams with 1 or more of the following: a maximal aortic gradient > 15 mm Hg, a mean aortic gradient ≥ 10 mm Hg, a maximal mitral gradient ≥ 5 mm Hg, a mean mitral gradient ≥ 2.5 mm Hg, a mitral or aortic insufficiency > 2/4, a pericardial effusion > 4 mm, or a right ventricle to right atria gradient ≥ 35 mm Hg. Indexed LV mass was not available because the height and weight were not systematically entered in the databank during the study period. From the remaining exams we analyzed all the diastolic function parameters readily available from pulse Doppler and tissue Doppler imaging (TDI) (E wave velocity, A wave velocity, E/A ratio and the ratio of E wave velocity to the early diastolic velocity of the lateral mitral annulus (E/e ratio) (if available). Measurements were routinely performed according to the standards of the American Society of Echocardiography, mostly by experienced technicians, cardiology residents and cardiologists.

The Institutional Committee on Human Research approved the study.

Statistical analysis

Statistical analysis was performed with SPSS 16.0 software. Linear regression tests were used to analyze the impact of age and sex on the different studied parameters. We also applied a univariate general linear model to verify if an interaction existed between age and sex for any of the studied parameters. Statistical significance was set at $p < 0.05$.

Results

A total of 14,298 patients were included in our analysis. There were 7,026 men (49.1%) and 7,272 women (50.9%) with a mean age of 58.53 ± 16.84 (SD) years old (Fig. 1). The youngest and oldest patients were respectively 7 years old and 98 years old. Results are summarized in Tables 1 and 2.

E/A ratio decreased with advancing age ($p < < 0.001$) both in men and women (Fig. 2) but there was no significant difference between both sexes ($p = 0.298$). A wave velocity increased significantly with age ($p < 0.001$) and was significantly different between both sexes. A wave velocity was higher in women ($p < 0.001$) and its progression with age was faster in women than in men ($p = 0.015$). We also observed a significant decrease in E wave velocity with aging ($p < 0.001$) and E wave velocity

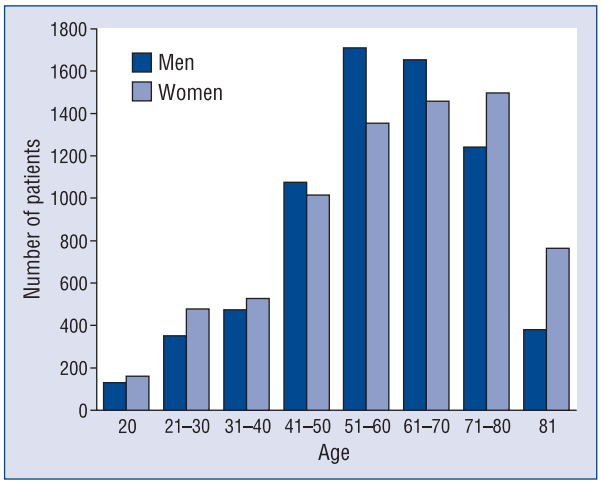

Figure 1. Patients distribution in function of their age and sex.

was also higher in women ($p < 0.001$) compared to men. Nevertheless, diminution of E wave velocity in function of age was the same in men and women ($p = 0.698$).

Diastolic function evaluation with TDI was not performed routinely until 2007 in our center so only 10% of our population had a reported e value. Nevertheless, it represents 1,457 patients with a calculable E/e ratio, including 230 patients younger than 40 years old. Interestingly, E/e increased progressively with age ($p < 0.001$) by regression analysis. Also, baseline values of E/e in men were lower than in women ($p < 0.001$) (Fig. 3). Finally, progression of E/e during aging process was the same for both men and women ($p = 0.348$). It is of interest to note that, after the age of 40, more than 10% of our patients had an E/e ratio higher

Table 1. Echocardiographic diastolic function parameter (E/A ratio*) in function of age and sex of patient.

Age	N	Median	5th centile:95th centile	10th centile:90th centile
≤ 20	294	2.0	1.2–3.4	1.3–2.9
21–30	830	1.7	1.1–2.9	1.2–2.5
31–40	1003	1.5	0.9–2.4	1.1–2.1
41–50	2093	1.3	0.8–2.1	0.8–1.8
51–60	3069	1.1	0.7–1.8	0.7–1.6
61–70	3118	0.9	0.6–1.6	0.7–1.4
71–80	2743	0.8	0.5–1.5	0.6–1.2
≥ 81	1148	0.7	0.5–1.4	0.5–1.1

*E/A ratio is not different between sexes ($p = 0.298$) but decreases significantly with age ($p < 0.001$); E/A — ratio of early to late mitral inflow diastolic velocities

Table 2. Echocardiographic diastolic function parameter (E/e ratio*) in function of age and sex of patient.

Age	N	Median	5th centile:95th centile	10th centile:90th centile
Men				
≤ 20	11	4.4	3.0–5.6	3.0–5.5
21–30	36	4.8	2.4–7.0	3.3–6.1
31–40	59	5.4	3.8–10.1	4.1–7.8
41–50	117	6.0	3.9–10.1	4.2–8.9
51–60	197	6.5	3.8–11.0	4.2–10.0
61–70	189	7.4	4.2–13.0	5.0–11.5
71–80	129	7.9	5.0–14.8	5.6–12.4
≥ 81	35	8.6	5.3–16.1	5.6–14.3
Women				
≤ 20	13	5.3	3.8–7.4	4.2–6.9
21–30	55	5.2	3.3–13.2	3.5–10.4
31–40	56	6.0	3.6–12.1	4.2–9.0
41–50	92	6.2	4.4–10.3	4.6–8.4
51–60	146	7.8	4.6–13.4	5.2–11.0
61–70	132	8.6	5.0–13.0	5.6–11.8
71–80	125	9.6	5.3–17.3	6.3–14.1
≥ 81	65	10.7	6.2–18.4	7.2–17.1

*E/e ratio is higher in women than in men ($p < 0.001$) and increases significantly with age ($p < 0.001$); E/e — ratio of early diastolic mitral ventricular filling velocity to early mitral annular velocity

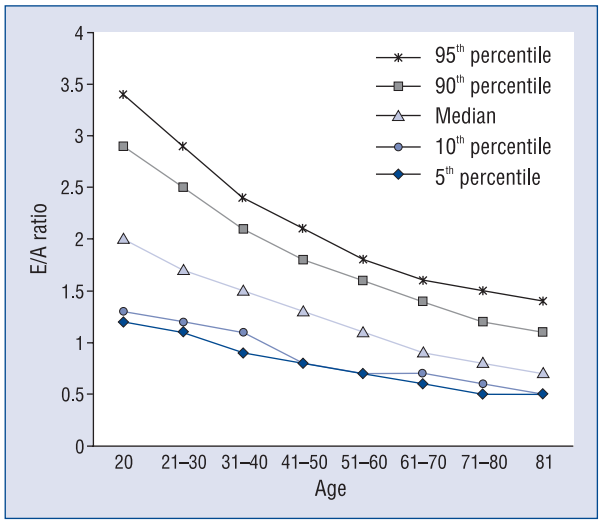

Figure 2. E/A ratio median in function of age of the patients. E/A ratio median values for all the patients for each decade of age from age < 20 to age > 80 years old with the 5th, 10th, 90th and 95th percentile for each value. E/A ratio decreases progressively with age ($p < 0.001$); E/A — ratio of early to late mitral inflow diastolic velocities.

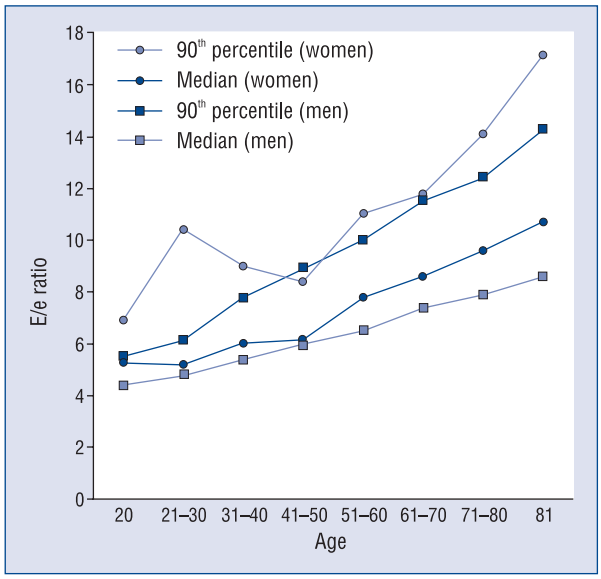

Figure 3. E/e ratio median in function of age and sex of the patients. E/e ratio median values for men and for women for each decade of age from age < 20 to age > 80 years old with the 90th percentile for each value. E/e ratio increases progressively with age ($p < 0.001$) and is higher in women than in men ($p < 0.001$); E/e — ratio of early diastolic mitral ventricular filling velocity to early mitral annular velocity.

than 8 and that, after the age of 70, this proportion increased to more than 50%.

Discussion

Effect of age on diastolic function

As expected, our results showed a significant effect of age on diastolic function parameters obtained by measurement of the mitral inflow velocity with pulsed Doppler echocardiography (Table 1). This was already noted in previous studies, but those studies focused on subgroups of older patients [5–9]. Our population included 2,127 patients younger than 40 years old and suggest that the influence of age on diastolic function parameters also equally apply to pre-forties subgroups.

Influence of age was also shown to be significant when diastolic function was assessed with TDI in our study (Table 2). Increase in E/e ratio with age was already described in the literature [5, 6, 9] but mostly in smaller cohorts of patients. Our study and Redfield et al. [9] study figure among the most important in terms of the size of their population and strengthen the linear relation between age and E/e ratio. In most studies trying to define normal E/e, patients were older than 45 years old and most were around 60 years old. Once again, our data have the advantage of including a considerable proportion of younger subjects (230 patients).

Ommen et al. [10] has shown that E/e higher than 15 was associated with elevated LV end-diastolic pressure (LVEDP). Based on the results of our study, we might consider that E/e values correlating with high LVEDP would actually be lower in younger patients. Further studies would be needed to verify this hypothesis and to assess if considering the patient's age could increase accuracy of E/e interpretation.

Currently accepted criteria [2] interpret an E/e ratio between 8 and 15 as being an intermediate zone that may or may not be associated with a high LVEDP. Our results show that a large proportion of our patients have E/e ratios between 8 and 15 and that this proportion increases significantly with age. In fact, more that 50% of our patients older than 70 years old have an E/e ratio higher than 8. It would be surprising that such a large proportion of patients have a high LVEDP and this may suggest that the lower cut-off value of 8 should probably be adjusted in function of age, as e decreases with aging [2]. It is interesting to note

that Tighe et al. [5] brought up the same doubt in a trial concerning 103 healthy individuals; although several older subjects in their study had E/e ratios > 8, they judge clinically unlikely that any of them had increased filling pressures. Moreover, in support of our findings are data from Ommen et al. [10] who showed that E/e is less predictive of LV filling pressures in patients with LVEF > 50% and data from Skaluba et al. [11] who noted that an E/e ratio < 10 is independently associated with a normal exercise tolerance regardless of the other filling pattern parameters. Like these authors, our work raises the possibility that the clinical relevant cut-off value for E/e ratio might be superior than 8, especially as age increases. It is therefore important to always correlate the data obtained from the echocardiography laboratory with the patient's symptoms, such as dyspnea and the overall evaluation of the cardiac function [2].

Effect of gender on diastolic function

Differences in diastolic function parameters obtained by pulsed Doppler between sexes were also described in past studies that suggested that women diminish their diastolic performance more quickly than men, even in normal aging process. In fact, Redfield et al. [9], Schirmer et al. [8] and De Sutter et al. [6] have all demonstrated this phenomenon and our results seem to correlate quite well with theirs. Moreover, a difference between sexes in diastolic function parameters obtained by TDI — that is a lower baseline E/e ratio in men — was also demonstrated from the 1,457 values available in our study. These findings are not considered in current guidelines probably because their clinical impact is unknown and further studies are required.

Limitations of the study

The retrospective model of our study with the lack of access to full clinical data was the major limitation. In fact, previous studies have demonstrated that diastolic function may vary with plenty of conditions, notably coronary heart disease, diabetes, hypertension and obesity. The data we used did not allow us to exclude those diseases so despite our efforts to select healthy subjects we cannot certify they were all and this may have affected our results.

Moreover, because data on indexed LV mass were not available for the study period, some patients with LV hypertrophy have probably been included in our cohort, possibly impacting our observations. However, De Sutter et al. [6] showed that patients with LV hypertrophy also have slightly higher E/e values for each age category and that LV mass index do not predict e or E/e. We are relatively confident that considering LV mass would have not change this tight relation like they showed.

Analysis of diastolic function is based on the integration of other parameters as well, such as left atrial volume index, transmitral deceleration time, isovolumic relaxation time, pulmonary venous reversal duration and TDI e velocity at the septal annulus — which have been shown to be less affected by mitral annular calcification. It would have been interesting to characterize the effect of age and gender on these parameters, but unfortunately, these data were not systematically collected in the past.

Finally, multiple skilled technicians acquired the results on different hardware and this may have induced some variability in our results. Nevertheless, we believe that the large number of patients included in our study partially offset most of these limitations.

Contemporary diastolic function assessment

Echocardiography societies have recently developed schemes that allow the gradation of the severity of diastolic dysfunction and the prediction of filling pressures. It has been shown to be a good predictor of all-cause mortality in a large epidemiologic study [12]. However, in clinical practice, the assessment of diastolic function remains complex given the large number of parameters to be acquired, which may be contradictory. Furthermore, parameters must be interpreted in light of the sex and age of the patient.

Conclusions

To our knowledge, this is the most imposing study, in terms of number of patients from first to tenth decade of life that were included, addressing the effect of age and gender on diastolic function. Not only does our study strengthen the influence of age on diastolic function parameters but it also reveal that the same influence apply to subgroups under 40 years old, a population not well studied before. Although TDI evaluation was available in only a limited proportion of our population, we were nevertheless able to show significantly higher value of E/e ratio in women and with advancing age raising question about the validity of actual proposed fixed limit value in these groups.

Globally, our results match the ones previously reported in the literature and emphasize the need

to consider age and sex when assessing diastolic function; one size fits all visibly does not apply to diastolic function evaluation. That said, our data should not be used as established gender and age--specific criteria for normality; in fact, despite our efforts to target a healthy population, inherent limitations of our retrospective design keep us from drawing that conclusion. Prospective trials are essential.

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Conflict of interest: none declared

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