Echocardiographic evaluation of centenarians in Trieste

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Background **Population aging has increased together with the need for cardiovascular care. Understanding the relevance of cardiovascular conditions in the very old is crucial to developing a specific and rationale therapeutic approach. Centenarians can be considered a model of successful aging, although the impact of cardiovascular disease in this population is still unclear.**

Aim **To evaluate the cardiovascular health status of a subset of centenarians enrolled in the Centenari a Trieste study and living in the province of Trieste to describe the prevalence of cardiovascular conditions among them.**

Methods **The current study included 20 individuals born before 1919 and living in the province of Trieste as of 1 May 2019. All centenarians were able to give consent and were subjected to an in-home complete clinical assessment focused on cardiovascular conditions, ECG and echocardiography.**

Results **The majority of centenarians were women (85%) and were not taking any chronic cardiovascular medication (55%). No centenarians had a history of ischemic heart disease while about one-third had signs suggestive of heart failure at examination (20%). Atrial fibrillation was present in 20% of individuals and conduction disorders were uncommon. Although the majority of individuals had a preserved left ventricular function, diastolic function was abnormal in 80% of enrolled centenarians that, however, was mild in 73% of cases.**

Conclusion **This is the second study to perform in-home echocardiography in centenarians and the first to characterize the cardiovascular status of centenarians living in Trieste. The majority of centenarians had asymptomatic diastolic dysfunction and were naïve from cardiovascular therapy. The recruitment of new individuals from the Trieste area is continuing to perform analyses on clinical, genetic and environmental factors that may predict greater longevity in this geographical context and unveil mechanisms that regulate cardiac aging associated with increased lifespan.**

Keywords: cardiovascular aging, centenarians, diastolic dysfunction, special populations

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Accepted 23 February 2020

Introduction

The world population is rapidly aging, and longevity might be considered as the most important achievement of modern medicine. The population of people aged 65 years or more is indeed projected to increase significantly in the European Union, reaching 149 million by 2050 with people aged 75–84 years expanding by 60.5%. More remarkably, the percentage very old people, aged 85 years or more, will rise between 2018 and 2050 by 130.3% with the number of centenarians projected to grow from close to 106 000 in 2018 to more than half a million by 2050.[1] However, the prolonged lifespan of individuals is still rarely associated with an increased healthspan.[2] With aging the prevalence of chronic conditions and the incidence of cardiovascular diseases (CVD) increases dramatically, reflecting the effect of the constant gait of time on the cardiovascular system.[3] Aging is indeed a major risk factor for CVD and a powerful predictor of adverse cardiovascular outcome.[4,5]

The mean age of the population has increased together with the need for cardiovascular care.[6] Although elderly individuals represent the majority of patients requiring cardiovascular clinical attention, old people have been often excluded from cardiovascular drug trials, reducing the evidence that supports their use in this population.[7] Thus, understanding the prevalence and pathophysiology of cardiovascular conditions in the growing aging population together with the mechanisms that regulate healthy

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aging is fundamental to precisely tailor the therapeutic approach and avoid overtreatment or mistreatment.

Centenarians, among very old people, represent a special population that may be considered as a model for successful aging.[8,9] Observational studies have assessed the role of potential protective factors that may have contributed to the longevity of centenaries[10,11]; moreover, some areas worldwide have been recognized as regions characterized by an exceptional longevity of their inhabitants,[12–14] suggesting the implication of genetic factors. Although much effort has been made to understand the pathophysiology of the cardiovascular system in advanced age,[3,15] how the interaction of genetic and environmental factors regulates cardiac aging in centenarians is still unclear. Furthermore, the prevalence of cardiovascular conditions in centenarians is still largely controversial, mainly because of limited studies and methodological issues.[16]

The Centenari a Trieste (CaT) study is a population-based study mainly focused on highlighting the risk and protective factors of brain aging of the centenarians living in Trieste and province, an Italian area where the percentage of centenarians is more than two-fold compared with the Italian average (0.07 vs. 0.03%).[17]

Within the 'Cat' project which includes 120 centenarians enrolled so far, we evaluated the cardiovascular health status of a subset of centenarians enrolled in the CaT study and living in the province of Trieste, who were alive between September 2017 and May 2019, to describe the prevalence of cardiovascular conditions among them.

Methods

Study population

The study population included individuals born before 1919 and living in the province of Trieste as on 1 May 2019. A request was sent to all centenarians' caregivers (relatives, general practitioners, nursing home or community service personnel) for permission to explain the study and enrol the subject. All participants signed an informed consent form. The study was conducted by a team of cardiologists who carried out all visits and clinical examinations at participants' homes or nursing homes. The study was approved by the institutional ethical committee and complied with the Declaration of Helsinki.

Clinical assessment

All patients underwent a complete clinical assessment. The clinical assessment included the anamnesis focused on the evaluation of the presence of cardiovascular risk factors, cardiovascular conditions including clinically diagnosed coronary artery disease, atrial fibrillation and heart failure, the presence of comorbidities and the use of medications. A full cardiovascular exam was performed with recording of vital signs and detection of symptoms suggestive of chronic heart failure. Furthermore, each individual was subjected to electrocardiographic and echocardiographic evaluation using portable devices, the latter conducted according to international guidelines.[18]

Echocardiographic evaluation

Left ventricular (LV) volume and LV ejection fraction (LVEF) were obtained by the Simpson biplane method. All volumes were indexed according to BSA. Transmitral diastolic velocities were measured using pulsed wave Doppler at the level of the mitral valve. Diastolic dysfunction was classified into three degrees.

LV filling was assessed by pulsed Doppler interrogation at the level of the mitral leaflets. The pattern of LV filling was classified as follows[18]:

(1) abnormal relaxation (grade I): E/A of less than 1 associated with E-deceleration time of at least 220 ms;
(2) 'pseudo-normal' (grade II): intermediate patterns;
(3) Restrictive Filling Pattern (grade III): in the presence of E-deceleration time of less than 120 ms or of E wave/A wave ratio of at least 2 associated with E-deceleration time of 150 ms, or less.

Right ventricular (RV) dysfunction was defined in the presence of a RV fractional area change less than 35%. Mitral regurgitation was assessed using a multiparametric approach by measuring the regurgitant jet area and vena contracta width using color-flow Doppler and, if feasible, by measuring the effective regurgitant orifice area by the proximal isovelocity surface area method. Left atrial end-systolic area was calculated from a four-chamber view. All measurements were obtained from the mean of three beats (patients in sinus rhythm) or of five beats (patients with atrial fibrillation).

Statistical analysis

Statistics of clinical and instrumental variables are expressed as means and SDs, medians and interquartile ranges or counts and percentages, as appropriate. Statistical analysis was performed with SPSS for Windows, version 23.0 (SPSS, Armonk, New York, USA).

Results

Study population

Between 1 September 2017 and 1 May 2019, 20 centenarians were included in the study. The majority (75%) of the centenarians in the cohort lived in a residential care center with medical and nursing assistance, while only five centenarians lived in their home with familiar assistance.

Clinical history and presentation at baseline

Main clinical characteristics of the study population are presented in Table 1. The majority of centenarians were women ($n = 17$, 85%; Table 1). No centenarians had a

Table 1 Clinical characteristics of the population

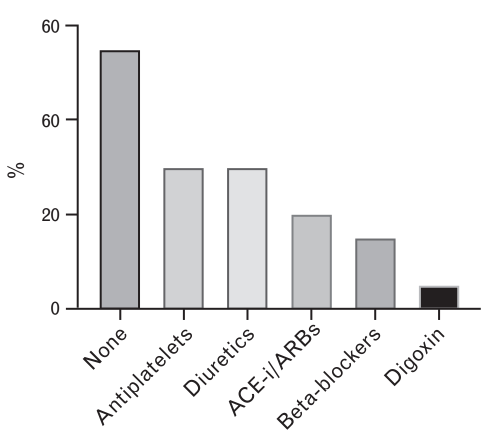
	Value
Age (years)	103 ± 2.4
Male sex, *n* (%)	3 (15)
BSA (m^2)	1.56 ± 0.1
SBP (mmHg)	118 ± 18
DBP (mmHg)	70 ± 13.0
NYHA I, *n* (%)	10 (50)
NYHA II, *n* (%)	7 (35)
NYHA III–IV, *n* (%)	3 (15)
Peripheral edema, *n* (%)	6 (30)
Pulmonary congestion, *n* (%)	6 (30)
Diabetes (%)	1 (5)
Coronary artery disease (%)	0 (%)
No chronic therapy	11 (55)
ACE inhibitors/ARBs, *n* (%)	4 (20)
Beta-blockers, *n* (%)	3 (15)
Antiplatelet therapy, *n* (%)	6 (30)
Digoxin, *n* (%)	1 (5)
Diuretics, *n* (%)	6 (30)

Values are expressed as mean ± SD or median with interquartile range as appropriate, and as percentage. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; NYHA, New York Heart Association.

history of ischemic heart disease (IHD) and only one subject (5%) had type 2 diabetes mellitus.

Medical therapy was limited in this population. The majority of the individuals (55%, $n = 11$) were not taking any chronic cardiovascular medication, whereas the remaining patients have a combination of either diuretics (30%, $n = 6$), antiplatelets (30%, $n = 6$), ACE inhibitors (20%, $n = 4$) or beta-blockers (15%, $n = 3$) (Fig. 1). Mean age of the population was 103 ± 2.4 years. At physical examination, individuals were normotensive with SBP of 118 ± 18 mmHg, while half of the population was in New York Heart Association (NYHA) class II or III. Approximately one-third of the centenarians ($n = 6$) had signs suggestive of heart failure (peripheral edema or pulmonary congestion) at examination.

Fig. 1



Cardiovascular drugs prescription at enrolment. The majority of subjects do not take any cardioactive drug. Data shown as percentage.

Table 2 ECG characteristics of the population

	Value
Heart rate (bpm)	71 ± 15
Atrial fibrillation, *n* (%)	4 (20)
PM implantation, *n* (%)	1 (5)
PQ (ms)	209 ± 29.3
QRS (ms)	102 ± 29.0
QT (ms)	402 ± 46.6
QTc (ms)	429 ± 38.4
RBBB, *n* (%)	4 (20)
LBBB, *n* (%)	1 (5)
Left ventricular hypertrophy-ECG, *n* (%)	1 (5)

LBBB, left bundle branch block; PM, pacemaker; RBBB, right bundle branch block.

Electrocardiographic and echocardiographic characteristics

The majority of the centenarians ($n = 16$, 80%) had sinus rhythm at electrocardiography, with a mean heart rate of 71 ± 15 bpm. Four centenarians had right bundle branch block, while only one had left bundle branch block (LBBB). Only one enrolled individual (5%) had a pacemaker-induced rhythm and four individuals had chronic atrial fibrillation (20%) (Table 2).

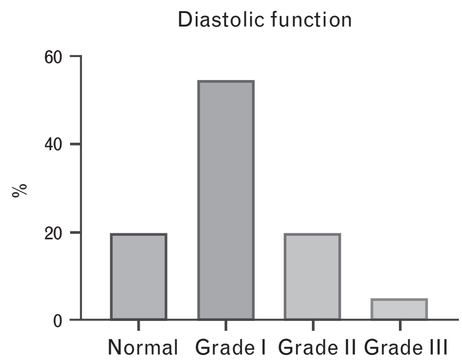
At the echocardiographic evaluation (Table 3), the LV end-diastolic diameter was 56 ± 7.6 mm with preserved

Table 3 Echocardiographic characteristics of the population

	Value
LVEDD (mm)	56 ± 7.6
LVESD (mm)	35 ± 4.2
IVS (mm)	1.1 ± 0.23
PW (mm)	1.0 ± 0.17
LVEDV (ml)	52 ± 9.5
LVESV (ml)	20 ± 4.8
LVEF (%)	60 ± 8.2
LAESA (cm^2)	23 ± 5.6
RAESA (cm^2)	18 ± 6.3
RV FAC (%)	58 ± 3.2
RV dysfunction (%)	1 (6)
Systolic PAP (mmHg)	41 ± 12.5
Mild MR (%)	8 (44)
Moderate MR (%)	2 (11)
Severe MR (%)	0 (0)
Normal diastolic function, *n* (%)	3 (17
Grade I diastolic dysfunction, *n* (%)	11 (55)
Grade II diastolic dysfunction, *n* (%)	4 (20)
Grade III diastolic dysfunction (RFP), *n* (%)	1 (5)
E/*e*′ ratio	17 ± 11
E/*e*′ ratio <10 (%)	3 (17)
E/*e*′ ratio >0 <15 (%)	9 (50)
E/*e*′ ratio >15 (%)	3 (33)
DT (ms)	227 ± 56.2
E/*A* ratio	0.78 ± 0.32
TAPSE (mm)	18.1 ± 3.4
IVCT	91.4 ± 25.4
IVRT	83.9 ± 24.1

DT, deceleration time; FAC, fractional area change; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; IVS, interventricular septum; LAESA, left atrial end-systolic area; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; PAP, systolic pulmonary artery pressure; PW, posterior wall; RAESA, right atrial end systolic area; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion.

Fig. 2



Diastolic function at echocardiographic evaluation. A high proportion of centenarians had abnormal diastolic function that, however, is mild. Data shown as percentage.

LV systolic function (main LVEF of 60 ± 8.2%). Only one patient had moderate LV systolic dysfunction.

At enrolment, only one centenarian (5%) showed an isolated restrictive LV filling pattern, while a high proportion of the centenarians had grade I diastolic dysfunction ($n = 11$, 55%) or pseudo-normal LV filling pattern ($n = 4$, 20%) (Fig. 2).

Approximately 17% of individuals ($n = 3$) had normal E/e' parameters. All those individuals were not on medical therapy.

No individuals presented severe valvular disease, while almost half of the group had mild mitral regurgitation and only two had a moderate mitral regurgitation. Approximately 95% of the individuals ($n = 17$) had tricuspid regurgitation, whereas only one had severe tricuspid regurgitation.

Finally, the presence of a RV dysfunction was found in only one individual with a registered mean fractional area change of 58 ± 3%.

Discussion

Clinical and electrocardiographic characteristics

The individuals that we have analyzed can be considered in relatively good health condition, especially considering their advanced age. Blood pressure was well controlled, only 1 centenarian out of 20 had a diagnosis of diabetes and no one had history of IHD. However, due to the particular state of this population, silent or asymptomatic IHD might not be entirely excluded. Moreover, even considering the challenging clinical assessment due to their limited exertional capacity, 50% of individuals were in NYHA class I. Nonetheless, the prevalence of signs of heart failure and the proportion of patients receiving diuretics (30%, respectively) suggested that at least half of the individuals were not symptomatic for cardiac failure or did not experience clinical decompensation. Alongside a previous Danish report, similar heart failure prevalence was observed in our population. However, the Danish population had a much higher prevalence of IHD.[19] This epidemiological contrast may be related to the small number of individuals enrolled in our study although differences in genetics background and environmental factors cannot be excluded.

ECG abnormalities were common in our population, even though we observed mostly minor conduction disturbances with mild prognostic implications. Indeed, the prevalence at ECG of signs of myocardial necrosis, atrial fibrillation and LBBB were infrequent if considering the very advanced age. These findings are in line with other studies reporting that the only ECG abnormality with a prognostic impact in this kind of population was the presence of atrial fibrillation.[20] Furthermore, the slight decline in function of the conduction tissue was highlighted by a high prevalence of first-degree atrioventricular block, with a medium atrioventricular conduction time of 209 ± 29 ms. However, only one patient required pacemaker implantation for conduction disturbances. These data suggest that despite atrioventricular disturbances being frequent in aged populations, those are not of prognostic implication if they are not associated with symptoms or to more advanced blocks requiring a pacemaker implantation. Increasing the number of individuals will allow future prognostic correlations to better define the role of our clinical and electrocardiographic findings, and possibly identify useful modifications in medical therapy to improve the prognosis and quality of life in this setting.

Echocardiographic analysis

The majority of the individuals analyzed present normal systolic function, in line with previous reports.[21] Although diastolic dysfunction is highly represented in our population (80%) compared with other studies,[21] the majority of those individuals were presenting only mild changes (73% grade I diastolic dysfunction). Pathophysiology of age-related diastolic dysfunction is multifactorial with myocardial stiffness secondary to cardiac fibrosis, titin isoform shifts and alteration in intracellular Ca^{2+} transients being recognized as the main mechanism.[22–26] Sedentary lifestyle with more bed rest deconditioning and an increase in sympathetic system activity seems to lead to progressive muscle atrophy that involves also the heart muscle, and may further compromise diastolic function.[27] An impairment of myocardial relaxation is an additional result of these structural changes connected with aging and hypertension. Even if its role in the age-related diastolic dysfunction has not been clearly defined, it may contribute to affect LV and left atrial pressure and so cause heart failure symptoms also in elderly individuals with preserved ejection fraction Heart Failure with Preserved Ejection Fraction (HFpEF).[28] The individuals whom we have enrolled, similarly to other reports, present moderate pulmonary hypertension while we observe a higher prevalence of grade I diastolic dysfunction.[21] Indeed, an abnormal relaxation pattern or grade I diastolic dysfunction, attributable to age-related myocardial stiffness, has been commonly described in elderly individuals. This kind of diastolic dysfunction characterized by a progressive decrease in E velocity and early diastolic deceleration slope with an increase in A velocity ($E/A < 1$) has in fact been defined as 'physiological', 'normal for age' or even better than 'expected' in this population.[29] Conversely, clinical reports suggest considering also in elderly individuals an E/A ratio more than 1 as an abnormal finding, possibly associated with a worse prognosis.[30] Our data were supported by the increased ratio of E/e' in individuals with diastolic dysfunction. Although the limited number of individuals is a major limitation, the relatively good performance of diastolic function in this population represents an interesting finding. Aging changes in diastolic function have broad implications for cardiovascular health in the elderly and understanding the molecular mechanisms that have preserved diastolic function in centenarians may be crucial to developing novel therapeutic strategies.

Pharmacological treatment

Approximately one in two of the individuals ($n = 11$, 55%) was not taking cardioactive drugs on a regular basis. Although clinical IHD was not detected, 30% of individuals were taking oral antiplatelets. Clinical history was not conclusive and we speculate that antiplatelet agents may have been prescribed in the past for the primary prevention of cardiovascular disease. Consistently with the frail status, antihypertensive agents and lipid lowering treatment were barely present, as expected in such an aged population. These findings are in line with a previous study demonstrating a sub-prescription of disease-modifying drugs in favor of symptomatic drugs (e.g. diuretics to improve symptoms in heart failure vs. anti-neurohormonal agents).[31]

Limitations

Despite the relatively high frequency of centenarians in the area, the absolute number of individuals is quite low and the majority of them are women. We cannot exclude that sex differences in this subgroup of patients may have played a role in determining the cardiovascular outcome.[32,33] Therefore, clinical characteristics might be genuinely applicable only in this specific subgroup of individuals. The small number of individuals is in part secondary to the limited availability of living centenarians during the study period. Furthermore, performing in-home clinical and instrumental cardiologic examination requires a coordinated team and resources. Prediction analysis on the lower incidence of adverse prognostic disease is somehow difficult and a possible selection bias might not be entirely excluded due to the rarity of these individuals.

Advanced imaging and biomarkers are not available in this population due to the particularly frail status and the setting of the analysis.

Finally, because of the limited number of individuals, genetic evaluation of this population has not been performed yet. The enrolment of new participants will allow a more comprehensive analysis of the balance between genetic and environmental factors in determining cardiovascular aging in this specific population.

Conclusion

To our knowledge, this is the second study to perform in-home echocardiography in centenarians and the first to characterize the cardiovascular status of centenarians living in Trieste, a city with a demographic structure that may be considered an ethnic melting pot because of the history and geographical location. Although the conclusions of this study are limited by the small number of individuals enrolled, the data that we have generated are in part in line with previous studies with some peculiarities. The vast majority of centenarians had asymptomatic diastolic dysfunction and were naïve from cardiovascular therapy. The recruitment of new individuals from the Trieste area is continuing to perform analyses on clinical, genetic and environmental factors that may predict greater longevity in this geographical context and unveil mechanisms that regulate the cardiac aging associated with increased lifespan.

Acknowledgements

We would like to thank ICGEB Trieste, Fondazione CR Trieste, Fondazione CariGO, Fincantieri for the financial support and all Trieste centenarians, their families, the general practitioners and the nursing home and community service personnel for taking time to participate.

Conflicts of interest

There are no conflicts of interest.

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