Changes in cardiac time intervals over a decade and the risk of incident heart failure

The Copenhagen City Heart Study

Alhakak, Alia Saed; Olsen, Flemming Javier; Skaarup, Kristoffer Grundtvig; Lassen, Mats Christian Højbjerg; Johansen, Niklas Dyrby; Espersen, Caroline; Abildgaard, Ulrik; Jensen, Gorm Boje; Schnohr, Peter; Marott, Jacob Louis; Søgaard, Peter; Møgelvang, Rasmus; Biering-Sørensen, Tor

Published in:
International Journal of Cardiology

DOI (link to publication from Publisher):
10.1016/j.ijcard.2023.05.018

Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

International Journal of Cardiology 386 (2023) 141–148

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Changes in cardiac time intervals over a decade and the risk of incident heart failure: The Copenhagen City Heart Study

Alia Saed Alhakak [a,1,*], Flemming Javier Olsen [a,1], Kristoffer Grundtvig Skaarup [a,1], Mats Christian Højbjerg Lassen [a,1], Niklas Dyrby Johansen [a,1], Caroline Espersen [a,1], Ulrik Abildgaard [a,1], Gorm Boje Jensen [b,1], Peter Schnohr [b,1], Jacob Louis Marott [b,1], Peter Søgaard [b,c,d,1], Rasmus Møgelvang [b,e,f,g,1], Tor Biering-Sørensen [a,b,h,1]

[a] Department of Cardiology, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark
[b] The Copenhagen City Heart Study, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark
[c] Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark
[d] Department of Clinical Medicine, University of Aalborg, Aalborg, Denmark
[e] Department of Cardiology, The Heart Center, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
[f] Institute of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[g] Cardiovascular Research Unit, University of Southern Denmark, Odense, Denmark
[h] Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

ARTICLE INFO

Keywords:
Cardiac time intervals
Heart failure
TDI-echocardiography

ABSTRACT

Background: The cardiac time intervals include the isovolumic contraction time (IVCT), the left ventricular ejection time (LVET), the isovolumic relaxation time (IVRT) and the combination of all the cardiac time intervals in the myocardial performance index (MPI) (defined as [(IVCT+IVRT)/LVET)]. Whether the cardiac time intervals change over time and which clinical factors that accelerate these changes is not well-established. Additionally, whether these changes are associated with subsequent heart failure (HF), remains unknown.
Methods: We investigated participants from the general population (n = 1064) who had an echocardiographic examination including color tissue Doppler imaging performed in both the 4th and 5th Copenhagen City Heart Study. The examinations were performed 10.5 years apart.
Results: The IVCT, LVET, IVRT and MPI increased significantly over time. None of the investigated clinical factors were associated with increase in IVCT. Systolic blood pressure (standardized β= − 0.09) and male sex (standardized β= − 0.08) were associated with an accelerated decrease in LVET. Age (standardized β=0.26), male sex (standardized β=0.06), diastolic blood pressure (standardized β=0.08), and smoking (standardized β=0.08) were associated with an increase in IVRT, while HbA1c (standardized β= − 0.06) was associated with a decrease in IVRT. Increasing IVRT over a decade was associated with an increased risk of subsequent HF in participants aged <65 years (per 10 ms increase: HR 1.33; 95%CI (1.02–1.72), p = 0.034).
Conclusion: The cardiac time increased significantly over time. Several clinical factors accelerated these changes. An increase in IVRT was associated with an increased risk of subsequent HF in participants aged <65 years.

1. Introduction

Cardiac structure and function change with normal aging, and these age-associated changes are influenced by lifestyle and cardiovascular diseases (1,2). The cardiac time intervals including the isovolumic contraction time (IVCT), the left ventricular ejection time (LVET), the isovolumic relaxation time (IVRT) are all closely related to cardiac function. The MPI is defined as [(IVCT+IVRT)/LVET] and theoretically combines information on systolic and diastolic function in one measure (3). Changes in the cardiac time intervals are sensitive markers of

* Corresponding author at: Cardiovascular Non-Invasive Imaging Research Laboratory, Department of Cardiology, Herlev and Gentofte Hospital, University of Copenhagen, Kildegårdsvej 28, Post 835, Hellerup 2900, Copenhagen, Denmark.
E-mail address: aliasaed@hotmail.com (A.S. Alhakak).
[1] All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ijcard.2023.05.018
Received 1 January 2023; Received in revised form 23 April 2023; Accepted 10 May 2023
Available online 12 May 2023

cardiovascular diseases. An increased IVCT has been shown to be associated with cardiovascular diseases, while a decreased LVET has been shown to be associated with poor cardiovascular outcomes in various different populations, including patients with heart failure (HF), ischemic heart disease and primary pulmonary hypertension (4–10). Both an increased as well as a decreased IVRT has been shown to be associated with adverse outcomes in patients with HF (11–13).

Current knowledge about the age-associated changes in the cardiac time intervals is based on cross-sectional studies that investigated the cardiac time intervals by different age-categories (3,14). Moreover, it is not well-established whether changes in the cardiac time intervals occur as a part of normal aging or only in the presence of cardiovascular diseases and risk factors. Thus, it is of relevance to investigate the longitudinal changes of the cardiac time intervals over time with repeated echocardiographic examinations. It is of clinical importance to identify the risk factors that accelerate changes of the cardiac time intervals. This could potentially guide risk factor modification and improve the understanding of the aging heart assessed by the cardiac time intervals.

The objectives of the current study were firstly to investigate the longitudinal changes of the cardiac time intervals in participants from the general population and to explore whether these changes occur as a part of normal aging in participants free of cardiovascular disease and risk factors. Secondly, to identify clinical risk factors that accelerate the changes of the cardiac time intervals. Thirdly, to assess whether the longitudinal changes in the cardiac time intervals are associated with an increased risk of subsequent incident HF.

2. Methods

2.1. Study population

The Copenhagen City Heart Study (CCHS) was designed as a prospective cohort study to identify cardiovascular risk factors among participants from the general population in Denmark (clinicaltrials.gov identifier.: NCT02993172). Information on the CCHS has been described in detail elsewhere (15). The current study investigated participants who had an echocardiographic examination including color tissue Doppler imaging performed in both the 4th study (CCHS4) and the 5th study (CCHS5). The CCHS4 was performed between 2001 and 2003 and the CCHS5 between 2011 and 2015.

Participants with lacking measurements of the cardiac time intervals at the baseline examination (CCHS4) or the follow-up examination (CCHS5) were excluded. This left a total of 1064 participants for the main analysis of investigating longitudinal changes of the cardiac time intervals. In order to examine whether the longitudinal changes occur as part of normal aging, a subgroup analysis was performed restricted to participants free of cardiovascular diseases. Therefore, participants with known cardiovascular diseases and risk factors at both the baseline visit (CCHS4) and the follow-up visit CCHS5) were excluded. A total of 368 participants were included for this subgroup analysis.

To investigate whether the longitudinal changes of the cardiac time intervals are associated with incident HF, an analysis was performed, where participants with known HF at the baseline visit (CCHS4) and the follow-up visit (CCHS5) were excluded. This This left a total of 1040 participants for inclusion in the prognostic analysis.

A detailed flow diagram of the study population and the exclusion process is displayed in supplemental Fig. S1.

Of the 1064 participants included in the main analysis 99% (n = 1053) were in sinus rhythm, while 1% (n = 11) had atrial fibrillation during the echocardiographic examination at the baseline visit (CCHS4). At the follow-up visit (CCHS5) 97% (n = 1035) were in sinus rhythm, while 3% (n = 29) had atrial fibrillation. At the baseline visit (CCHS4) none of the participants had heart valve disease, while 1% (n = 13) had heart valve disease at the follow-up visit (CCHS5). None of the 368 participants included in our subgroup analysis had atrial fibrillation, heart valve disease or heart failure at the baseline visit nor follow-up visit.

The CCHS was conducted in accordance with the 2nd Declaration of Helsinki, and approved by the Regional Ethics Committee. Written informed consent was collected from all the participants before the examination. The participants underwent a general health examination at both CCHS4 and CCHS5, which included a physical examination, self-administered questionnaire and blood samples.

Information on physical activity level, socioeconomic status, psychosocial, and smoking status were acquired from the self-administered questionnaire. Definitions of hypertension, diabetes mellitus, hypercholesterolemia and prevalent ischemic heart disease have previously been described (16,17).

2.2. Echocardiography

In the CCHS4 the echocardiographic examinations were performed by three experienced sonographers, while four experienced sonographers performed the echocardiographic examinations in the CCHS5. The echocardiographic examinations were performed according to a predetermined protocol by the use of GE Healthcare ultrasound machines. Vivid 5 ultrasound machines were used in the CCHS4, while Vivid 9 ultrasound machines were used in the CCHS5. The echocardiograms were analyzed offline with commercially available software (EchoPac GE Healthcare, Horten Norway), version 2008 was used in the CCHS4, while version 113 was used in the CCHS5 (17).

The LVEF was estimated by 1 observer on the basis of wall motion score index (16). In the parasternal long-axis view at end-diastole, the LV dimensions were measured including interventricular septal diameter, LV internal diameter, and LV posterior wall diameter. Based on these measurements, the LV mass index (LVMI) was calculated by dividing the LV mass with the body surface area (BSA) (18).

The left atrial (LA) volume was measured at end-systole using the biplane area-length method and indexed to BSA to obtain the left atrial volume index (LAVI) (18).

Peak mitral inflow velocities were obtained using pulsed-wave Doppler including peak velocity of early (E) and atrial (A) diastolic filling and deceleration time of the *E*-wave.

The peak longitudinal early diastolic tissue velocity (e') was obtained using color TDI. The average values of e' were used to calculate E/e'.

LV speckle tracking echocardiography was performed in the 3 apical views and global longitudinal strain (GLS) was calculated as an average peak strain from the 3 apical views. This has previously been described in detail (19).

2.3. Tissue doppler imaging

Color TDI was used to obtain the cardiac time intervals from the 4-chamber view at the highest possible frame rate. In the CCHS4 the median frame rate was 122 frames per second [25th to 75th percentile: 96–133 frames per second], while the median frame rate was 164 frames per second [25th to 75th percentile: 162–167 frames per second] in the CCHS5. The cardiac time intervals were measured directly from the color diagram by placing a 2–4 cm straight M-mode line through the septal half of the anterior mitral valve leaflet (Supplemental Fig. S2).

The mitral valve closure (MVC) was measured at the color shift from blue/turquoise to red at end-diastole. The aortic valve opening (AVO) was measured at the color shift from blue to red at the beginning of the systole. The aortic valve closure (AVC) was measured at the color shift from red to blue at end-systole. The mitral valve opening (MVO) was measured at the color shift from red-orange to yellow.

The cardiac time intervals were defined as follows: The IVCT as the time interval from the MVC to AVO, the LVET as the time interval from the AVO to AVC, and the IVRT as the time interval from the AVC to MVO. This method has previously been described elsewhere (20–22).

2.4. Follow-up and outcome

The primary outcome was incident HF, and the competing event was all-cause death. The endpoints were collected in July 2018 from the Danish National Board of Health's National Patient Registry and the Danish Registry of Causes of Death using International Classification of Diseases, Tenth Revision codes (ICD-10).

2.5. Statistics

The distribution of continuous variables was assessed using histograms and QQ-plots. Baseline characteristics were reported as mean ± standard deviation (SD) for continuous Gaussian distributed variables, and continuous non-Gaussian distributed variables were reported as medians with 25th to 75th percentiles. Categorical variables were reported as frequencies and percentages. The changes in the cardiac time intervals (Δ values) were calculated as the difference between follow-up values and baseline values. Paired student's *t*-test was used to test for significant difference between follow-up values and baseline values.

Univariable and multivariable linear regression analyses were performed to investigate the impact of clinical, paraclinical, socioeconomic, and psychosocial factors on the changes in the cardiac time intervals. Standardized beta coefficients were reported. The univariable model was adjusted for the respective baseline value of the investigated cardiac time interval in order to adjust for regression to the mean. The multivariable regression model was adjusted for baseline value of the investigated cardiac time interval, age, sex, systolic blood pressure, diastolic blood pressure, body mass index (BMI), smoking, total plasma cholesterol, HbA1c, eGFR, resting heart rate, and previous ischemic heart disease. Test for collinearity was performed.

Restricted cubic spline regression models were constructed to illustrate the relationship between the dependent variables (Δ values of the cardiac time intervals) and continuous independent variables. The number of knots for each spline was determined according to the lowest values of Akaike information criterion (AIC).

Cox proportional hazard regression analyses were performed to investigate whether changes in the cardiac time intervals were associated with incident HF. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. Test for effect modification was performed, and a significant effect modification was found between IVRT and age at the baseline visit (CCHS4). Therefore, Cox regression analyses were performed for two age groups (<65 and ≥ 65 years). Due to the low number of events, the extent of the multivariable analysis was limited. Hence, the multivariable models were performed with stepwise increase in confounding variables from the baseline visit. Model 1 was adjusted for sex, BMI, hypertension, and diabetes. Model 2 was adjusted for sex, BMI, hypertension, diabetes, previous ischemic heart disease, and resting heart rate. Model 3 was adjusted for sex, BMI, hypertension, diabetes, previous ischemic heart disease, resting heart rate, E/e', and LVEF<50%. The assumptions of proportional hazards in all models were tested using the Schoenfeld residuals.

Restricted cubic spline models were constructed based on Poisson regression to estimate the incidence rate of the outcome. The number of knots were selected to minimize the values of AIC.

Competing-risk analyses were performed according to the method of Fine and Gray in order to account for death as a competing event. Competing risk Cox proportional hazard regression analyses were used to calculate subdistribution hazard ratios (SHR).

The prognostic strength of the examined echocardiographic parameters was assessed by calculating Harrell's C-statistics from Cox regression models.

Receiver operating characteristic curve was constructed for IVRT in the effort to identify the optimal cutoff value with the highest sensitivity and specificity for predicting the risk of HF.

The statistical analyses were conducted using STATA SE version 15.1 (StataCorp, College Station, Texas). All *p*-values <0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

The baseline characteristics for the study population at the baseline visit (CCHS 4) are shown in supplemental Table S1. The mean age was 52 ± 14 years, and 44% (n = 471) were male. The mean systolic and diastolic blood pressure were 129 ± 21 mmHg and 78 ± 12 mmHg, respectively, and mean resting heart rate was 66 ± 11 beats per minute.

3.2. Longitudinal changes of the cardiac time intervals

During the median follow-up of 10.5 years (25th to 75th percentile: 10.2–10.9 years), the IVCT significantly increased by 5 ± 15 ms, the LVET increased significantly by 2 ± 29 ms, the IVRT increased significantly by 12 ± 22 ms. Accordingly, the MPI increased significantly by 0.05 ± 0.12. In participants free of cardiovascular diseases (n = 368), the IVCT, IVRT, and MPI also increased. However, the LVET did not change. Table 1 shows the absolute differences between baseline values and follow-up values of the cardiac time intervals.

3.3. Accelerators of changes in the cardiac time intervals

In univariable and multivariable linear regression models none of the investigated factors were associated with an increase in IVCT (Fig. 1A and 2A). In univariable linear regression, several factors were associated with changes in LVET. Higher age, male sex, higher systolic blood pressure, and higher diastolic blood pressure were associated with an accelerated decrease in LVET. In contrast, longer education attenuated the decrease in LVET (Fig. 1B). However, after multivariable adjustment, systolic blood pressure (standardized β= − 0.09, p = 0.043) and male sex (standardized β= − 0.08, p = 0.020) remained significant accelerators of decrease in LVET (Fig. 2B). In univariable linear regression, several factors were associated with changes in IVRT. Higher age, male sex, higher systolic blood pressure, higher diastolic blood pressure, and smoking were associated with accelerated increase in IVRT, while longer education and higher eGFR were associated with accelerated decrease in IVRT (Fig. 1C). Of note, the impact of age on ΔIVRT was pronounced until approximately 60 years (Supplemental Fig. S3). However, after multivariable adjustment, age (standardized β=0.26, p < 0.001), male sex (standardized β=0.06, p = 0.044), diastolic blood pressure (standardized β=0.08, p = 0.030), and smoking (standardized β=0.08, p = 0.006) remained significant accelerators of increase in IVRT, while a higher level of HbA1c (standardized β= − 0.06, p = 0.039) was a significant accelerator of decrease in IVRT (Fig. 2C). In univariable linear

Table 1
Changes in the cardiac time intervals.

Cardiac time intervals	Baseline values	Follow-up values	Absolute difference	P-value
Participants included in the study (n = 1064)				
IVCT, ms	36 ± 13	41 ± 12	5 ± 15	<0.001
LVET, ms	287 ± 24	289 ± 28	2 ± 29	0.011
VRT, ms	97 ± 20	109 ± 21	12 ± 22	<0.001
MPI	0.47 ± 0.11	0.52 ± 0.11	0.05 ± 0.12	<0.001
Participants free of cardiovascular disease (n = 368)				
IVCT, ms	35 ± 12	41 ± 10	6 ± 14	<0.001
LVET, ms	291 ± 20	293 ± 24	2 ± 23	0.18
IVRT, ms	88 ± 18	102 ± 19	14 ± 19	<0.001
MPI	0.43 ± 0.09	0.49 ± 0.09	0.07 ± 0.10	<0.001

Data are presented as mean ± SD.
IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; LVET, left ventricular ejection time; MPI, myocardial performance index.

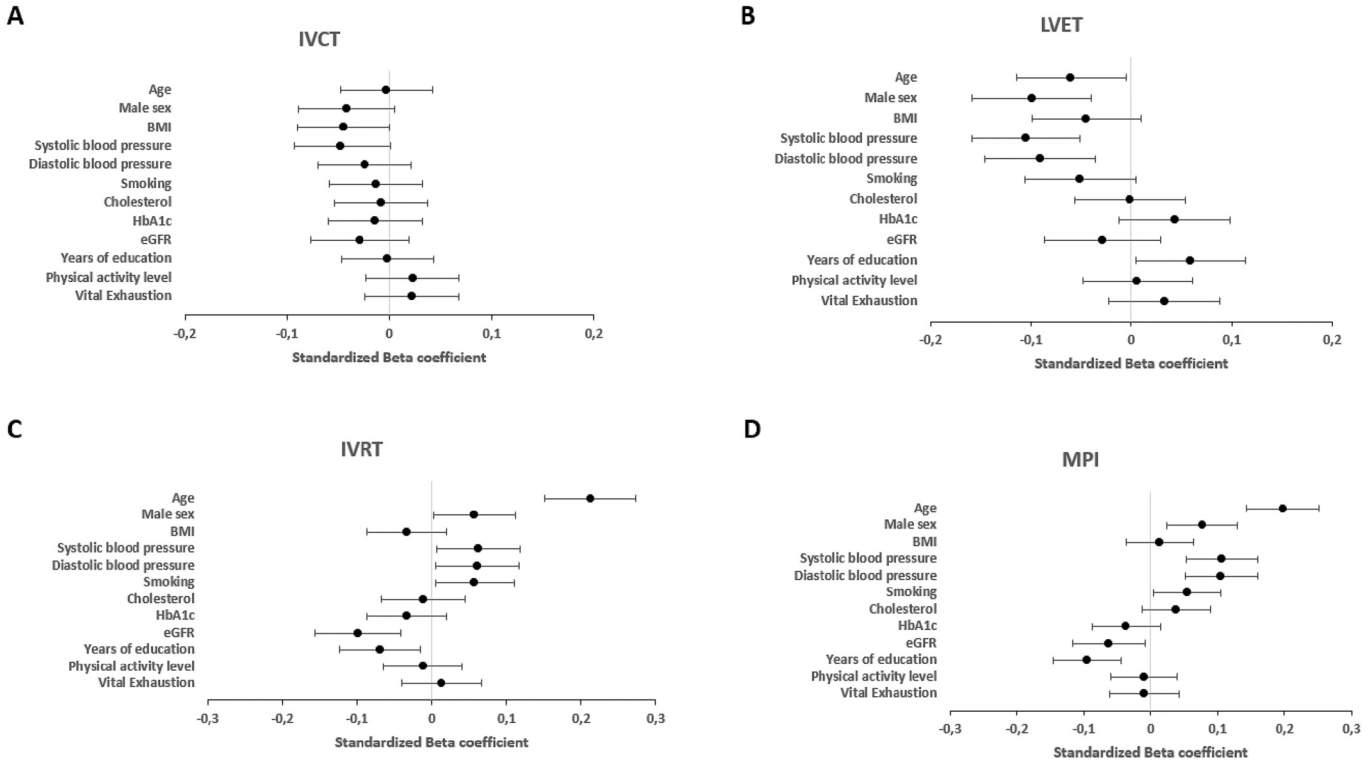

Fig. 1. Forest plots displaying the impact of clinical, paraclinical, socioeconomic and psychosocial factors on changes in the cardiac time intervals by standardized beta coefficients: IVCT (A), LVET (B), IVRT (C), MPI (D). The univariable models were adjusted for the respective baseline value of the investigated cardiac time interval.
IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; LVET, left ventricular ejection time; MPI, myocardial performance index.

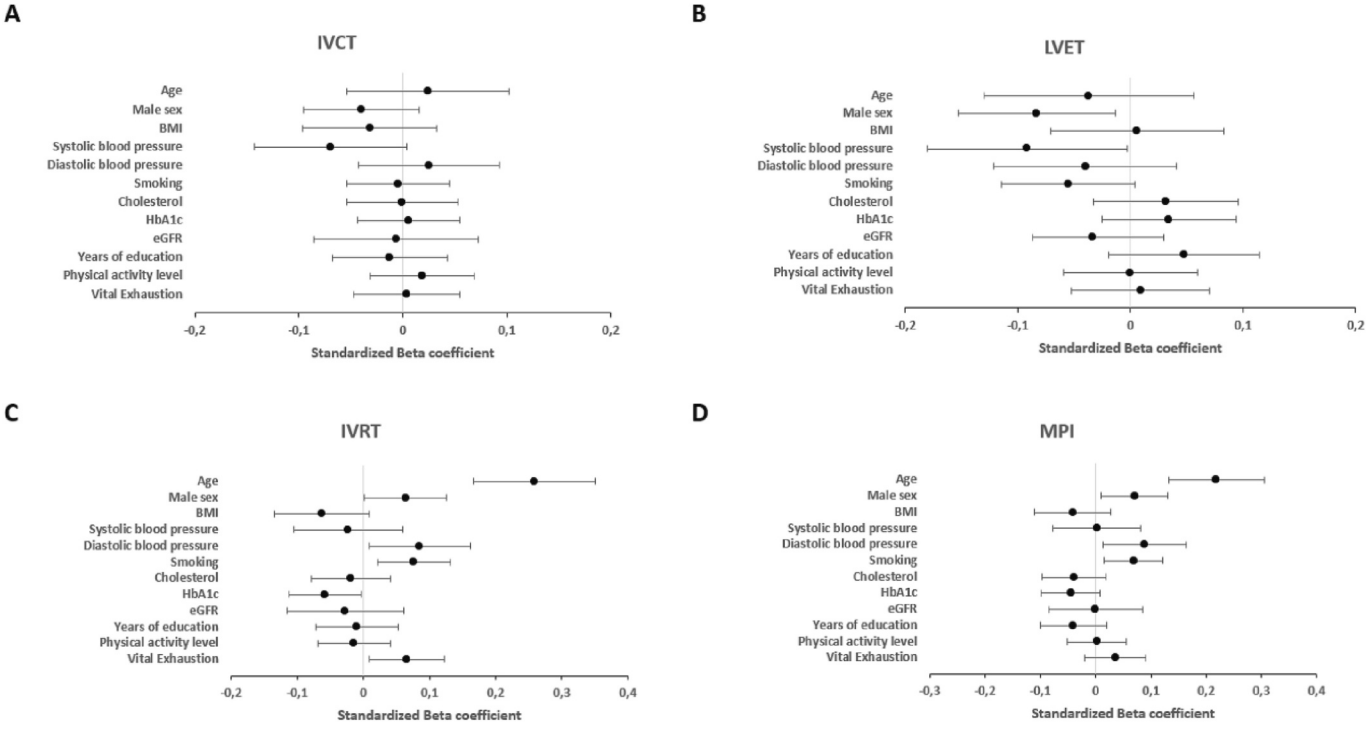

Fig. 2. Forest plots displaying the multivariable models estimated by standardized beta coefficients: IVCT (A), LVET (B), IVRT (C), MPI (D). The multivariable models were adjusted for baseline value of the investigated cardiac time interval, age, sex, systolic blood pressure, diastolic blood pressure, BMI, smoking, total plasma cholesterol, HbA1c, eGFR, resting heart rate, and previous ischemic heart disease.
BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin;
IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; LVET, left ventricular ejection time; MPI, myocardial performance index.

regression, the following factors were accelerators of increase in MPI: higher age, male sex, higher systolic blood pressure, higher diastolic blood pressure, and smoking. In contrast, longer education and higher eGFR, attenuated the increase in MPI (Fig. 1D). However, after multivariable adjustment, age (standardized β=0.22, $p < 0.001$), male sex (standardized β=0.07, $p = 0.021$), diastolic blood pressure (standardized β=0.09, $p = 0.020$), and smoking (standardized β=0.07, $p = 0.011$) remained significant accelerators of increase in MPI (Fig. 2D). Physical activity was not associated with changes in the cardiac time intervals in univariable and multivariable linear regression models.

3.4. Prognostic value of longitudinal changes in the cardiac time intervals

A total of 1040 participants were included in the prognostic analysis. During a median follow-up of 6.1 years (25th to 75th percentile: 4.8–6.7 years), 37 (3.6%) participants developed HF. The prognostic value of ΔIVRT was significantly modified by age at the baseline visit ($p = 0.035$ for interaction; Fig. 3). After adjusting for sex, BMI, hypertension, diabetes, previous ischemic heart disease, resting heart rate, E/e', and LVEF<50%, ΔIVRT predicted HF in participants aged <65 years (per 10 ms increase: HR 1.33; 95%CI (1.02–1.72), $p = 0.034$; Supplemental Table S2, Model 3). In contrast, ΔIVRT did not predict HF in participants aged ≥65 years, when adjusting for the same clinical and echocardiographic variables (per 10 ms increase: HR 0.95; 95%CI (0.68–1.34), $p = 0.79$; Supplemental Table S2, Model 3).

The results for ΔIVRT remained unchanged in competing-risk analysis with all-cause death as a competing event, when adjusting for the same clinical and echocardiographic variables in participants aged <65 years (per 10 ms increase: SHR 1.57; 95%CI (1.01–2.45), $p = 0.047$) and in participants aged ≥65 years (per 10 ms increase: SHR 0.98; 95%CI (0.74–1.31), $p = 0.90$).

ΔIVCT, ΔLVET, and ΔMPI were not significantly associated with incident HF.

The C-statistics for IVRT was 0,58, for E/A it was 0,72 and for E/e' it was 0,63.

We determined the optimal cutoff for predicting the risk of HF. The optimal cutoff for predicting HF was determined from the receiver operating characteristic curve and was found to be 123 ms for IVRT.

4. Discussion

This is the first study to investigate the longitudinal changes of the cardiac time intervals in participants from the general population based on echocardiographic examinations performed more than a decade apart from each other. The relevant findings of the current study were: 1) The cardiac time intervals including IVCT, LVET, IVRT, and MPI increased significantly over time in participants from the general population 2) In participants free of cardiovascular diseases and risk factors, the LVET did not increase. However, the IVCT, IVRT, and MPI increased significantly. 3) None of the investigated risk factors were associated with increase in IVCT. Systolic blood pressure and male sex were associated with an accelerated decrease in LVET. Age, male sex, diastolic blood pressure, and smoking were associated with an increase in IVRT, while HbA1c was associated with a decrease in IVRT. Age, male sex, diastolic blood pressure, and smoking were associated with an increase in MPI. 4) An increase in IVRT was associated with an increased risk of subsequent HF in participants aged <65 years at the baseline visit.

4.1. Longitudinal changes of the cardiac time intervals

In participants free of cardiovascular diseases and risk factors, we found that all the cardiac time intervals increased significantly over time except the LVET. This is in agreement with previous cross-sectional studies that investigated the changes of the cardiac time intervals by different age-categories in participants from the general population (3,14). However, when we considered the entire study population, a small but significant increase in LVET was observed. Conflicting results regarding the change of LVET over time have been reported. A previous cross-sectional study in participants from the general population ($n = 389$) aged 56.1 ± 11.8 years found that the LVET decreased, while the IVCT and IVRT increased (23). Participants with ECG abnormalities and poor image quality were excluded, while participants with known cardiovascular disease and risk factors were not excluded. The LVET was measured from the onset to the end of the aortic Doppler flow, and the total LVET was reported as LVET multiplied by heart rate. The observed decrease in LVET may be due to the presence of cardiovascular diseases and risk factors and not only higher age. Another study, which focused on elderly participants ($n = 512$) aged 60 to 90 years found that the LVET increased with aging (24). The participants with known HF and those who used digitalis were excluded, while participants with other cardiovascular diseases and risk factors were not excluded. The LVET was measured from the indirect carotid tracing and was defined as the interval from the beginning of the upstroke and the trough of the incisura. The different methods used to obtain LVET can explain the differences between the two abovementioned studies and our study findings regarding the change of LVET.

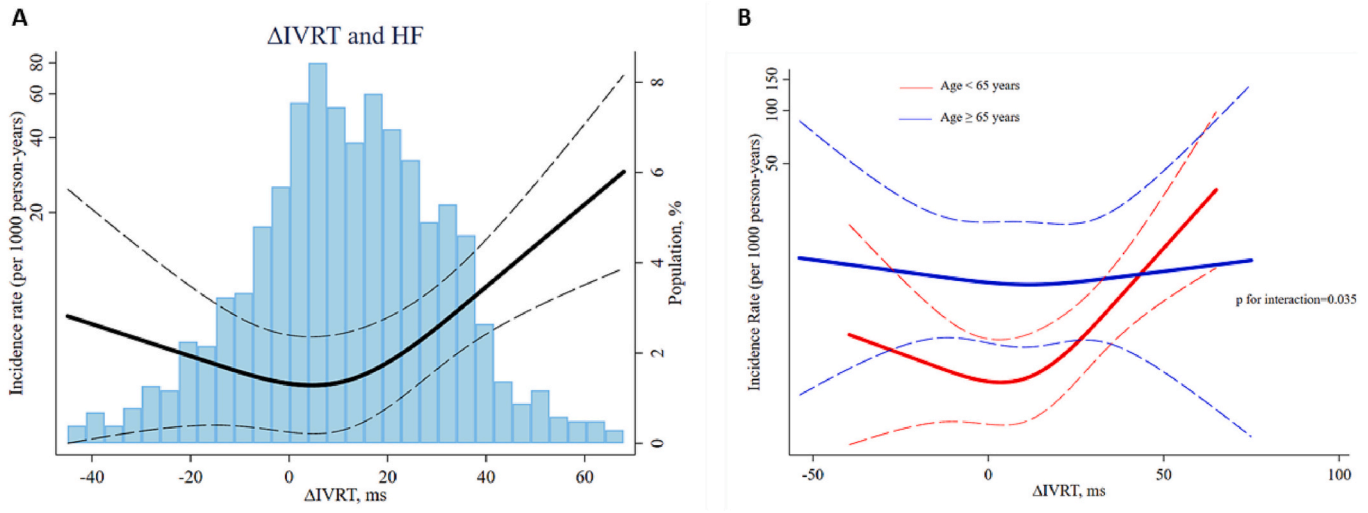

Fig. 3. Association between ΔIVRT and risk of HF Displaying the incidence rate of HF (events per 1000 person-years) according to ΔIVRT with 95% confidence intervals in the entire study sample (A) and stratified by age groups (B). The models are adjusted for baseline value of IVRT.

4.2. Accelerators of changes in the cardiac time intervals

The most impactful accelerator of a decrease in LVET was systolic blood pressure. It has previously been demonstrated that LVET was decreased in patients with untreated systemic hypertension. However, the decreased LVET in untreated hypertension was reversible, since LVET returned to normal after a relatively brief period of treatment with antihypertensive drugs (25).

We found that male sex was an accelerator of a decrease in LVET and an increase in IVRT, which is in line with previous studies that have reported that females have longer LVET and males have longer IVRT (26,27). The IVRT is a measure that is used to assess LV diastolic function and is bidirectional in the progression of diastolic function, since IVRT is increased in patients with impaired LV relaxation, but with normal LV filling pressures. However, when the left atrial pressure increases, the IVRT decreases (28).

In the current study we found that the most impactful accelerator of an increase in IVRT was age, which is consistent with previous studies demonstrating that aging was accompanied by an increase in IVRT (14,23,29). This age-associated increase in the IVRT is caused by a slowed myocyte relaxation due to the fact that the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA)-mediated calcium uptake declines with aging (30).

Higher levels of HbA1c were associated with a decrease in IVRT, which is in agreement with previous findings. In patients with diabetes mellitus type 1 ($n = 1088$), it has been reported that higher levels of HbA1c were associated with a decrease in IVRT (31). One of the pathophysiological mechanisms for development of the restrictive filling pattern in patients with diabetes mellitus is hyperglycaemia (32).

We found that smoking was associated with an increase in IVRT, which is in line with previous findings. A study investigated the chronic effects of smoking on diastolic function parameters and compared smokers ($n = 69$) with non-smokers ($n = 30$). The IVRT was significantly increased in smokers when compared to non-smokers (33). Several pathophysiological mechanisms are involved in the development of diastolic dysfunction in smokers. Smoking has direct effects on the myocardium and causes cellular damage, which is called “Smoke cardiomyopathy” (34). This leads to an increase in LV stiffness. Another possible mechanism is that smoking causes endothelial dysfunction through decreased production of endothelial nitric oxide (35).

4.3. Prognostic value of longitudinal changes in the cardiac time intervals

The change in IVRT between the examination at baseline and follow-up visit was associated with an increased risk of subsequent HF in participants who were < 65 years at the baseline visit.

This may be due to the fact that an increase in IVRT was pronounced until approximately age 60 years as displayed in supplemental Fig. S3. This age-associated increase in IVRT may contribute to the development of HF, since the increase in IVRT is associated with the progression of diastolic function (29).

A previous study investigated the changes in diastolic function over time based on two echocardiographic examinations performed 4 years apart. Diastolic function was assessed by pulsed-wave Doppler. The IVRT was not assessed in this study. The prevalence of diastolic dysfunction increased and was associated with development of HF during 6 years of subsequent follow-up (36). Similar to our findings it was found that age was associated with the development of diastolic function. However, in contrast to our study they found that age 65 years or older was associated with the development of subsequent HF, while we found that age 65 years or below was associated with the development of HF. This difference between the specific age category may be due to the fact that the mean age of participants included in the study was 61 ± 9.5 years at first examination, while the mean age of the participants included in our study was 52 ± 14 years.

Several pathophysiological mechanisms are involved in the development of diastolic dysfunction in HF including changes in myocardial relaxation, changes in elastic recoil, ventricular and diastolic stiffness (37). Furthermore, it has recently been demonstrated that abnormalities in the systemic vasculature, endothelium, adipocytes, and skeletal muscle also play an important role in the development of diastolic dysfunction in HF (38).

In the current study we could not assess whether the association between ΔIVRT and HF was due to HF with reduced ejection fraction or HF with preserved ejection fraction (HFpEF). However, it is recognized that patients with HF have abnormalities in both systolic and diastolic function (39).

HF develops stepwise, from risk factors that predispose to the development of HF, progressing to asymptomatic impaired LV function, and finally symptomatic HF (40). Therefore, in an aging population with increasing prevalence of HF (41), it is of clinical importance to identify early signs of HF before the development of fulminant disease. Changes in the IVRT can help quantify the risk of future HF. Furthermore, being able to identify risk factors that accelerate changes of the cardiac time intervals could potentially guide risk factor modification in order to prevent or delay the progression of changes in the cardiac time intervals. Using the TDI M-mode method, the cardiac time intervals can be obtained fast, easily, accurately and with high reproducibility (20–22). Moreover, by the use of the TDI M-mode method, the cardiac time intervals can be obtained regardless of heart rhythm, whereas other methods (pulsed-wave Doppler and pulsed-wave TDI) cannot obtain the cardiac time intervals in patients with atrial fibrillation due to the absence of an A wave or a' wave (22).

Obesity may have significant effect on image quality. However, by the use of the TDI M-mode method the cardiac time intervals can be obtained even when it is difficult to obtain echocardiograms with good image quality. The mitral valve is often easy to visualize, even when image quality is inadequate due to the fact that the mitral valve is perpendicular to the ultrasound beam (7).

Both E/A and E/e' had higher C-statistics than IVRT. However, the IVRT may be a valuable measure, since different echocardiographic measures may be used to identify particular high-risk individuals. Based on our findings, we suggest to include an assessment of the cardiac time intervals using the TDI M-mode method, when performing routine echocardiographic examinations. We propose using a cutoff of 123 ms for IVRT, when this measure is used for predicting the risk of HF in participants from the general population.

4.4. Study limitations

The findings of the current study should be viewed in context of potential limitations. The echocardiographic examinations were performed by experienced sonographers in both the CCHS4 and the CCHS4. We do not have data available regarding the interindividual variation between sonographers and cardiologists. The echocardiographic examination at baseline (CCHS4) and follow-up (CCHS5) were performed with different ultrasound machines and different versions of the post-processing software were used to analyze the echocardiograms. However, these factors are unavoidable due to the fact that the echocardiographic examinations were performed more than a decade apart from each other.

Unfortunately, we do not have data available regarding the type of the antihypertensive medication. Hence, the effect of the specific antihypertensive medication on heart rate and echocardiographic parameters could not be assessed.

Due to the low number of events in the prognostic analysis, the multivariable models may be subject to potential overfitting. However, when the multivariable models are used to demonstrate adequate control of confounders, this approach can be acceptable (42).

The HF diagnosis was obtained from the Danish nationwide registries using ICD-10 codes. It is not specified as either HFrEF or HFpEF. The HF diagnosis has been validated in two recent studies with positive

predictive values of 76% and 100% (43,44). However, using ICD-10 codes for HF diagnosis is not accurate as using adjudicated endpoints.

5. Conclusion

In the general population, the cardiac time intervals including IVCT, LVET, IVRT, and MPI increased significantly with aging. None of the investigated clinical factors accelerated the increase in IVCT. Decrease in LVET was accelerated by systolic blood pressure and male sex. Increase in IVRT was accelerated by age, male sex, diastolic blood pressure, and smoking, while decrease in IVRT was accelerated by higher levels of HbA1c. The change in IVRT was associated with an increased risk of subsequent HF in participants aged <65 years at the baseline visit.

Funding

ASA was funded by a research grant from the Gangsted Foundation. The sponsor had no role in the study design, data collection, data analysis, data interpretation, or writing of the article.

CRediT authorship contribution statement

Alia Saed Alhakak: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Flemming Javier Olsen:** Investigation, Writing – review & editing. **Kristoffer Grundtvig Skaarup:** Investigation, Writing – review & editing. **Mats Christian Højbjerg Lassen:** Investigation, Writing – review & editing. **Niklas Dyrby Johansen:** Writing – review & editing. **Caroline Espersen:** Writing – review & editing. **Ulrik Abildgaard:** Writing – review & editing. **Gorm Boje Jensen:** Project administration, Writing – review & editing. **Peter Schnohr:** Project administration, Writing – review & editing. **Jacob Louis Marott:** Methodology, Writing – review & editing. **Peter Søgaard:** Project administration, Writing – review & editing. **Rasmus Møgelvang:** Project administration, Writing – review & editing. **Tor Biering-Sørensen:** Supervision, Conceptualization, Methodology, Investigation, Project administration, Writing – review & editing.

Declaration of Competing Interest

Tor Biering-Sørensen reports receiving research grants from Sanofi Pasteur and GE Healthcare, being a Steering Committee member of an Amgen financed and a Boston Scientific financed trial, on advisory boards for Sanofi Pasteur and Amgen, and speaker honorariums from Novartis, Sanofi Pasteur, and GSK. The remaining authors have nothing to disclose.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.05.018.

References

[1] E.G. Lakatta, Cardiovascular regulatory mechanisms in advanced age, Physiol. Rev. 73 (2) (1993 Apr) 413–467.
[2] E.G. Lakatta, So! What's aging? Is cardiovascular aging a disease? J. Mol. Cell. Cardiol. 83 (2015 Jun) 1–13.
[3] T. Biering-Sørensen, R. Mogelvang, M.C. de Knegt, F.J. Olsen, S. Galatius, J. S. Jensen, Cardiac time intervals by tissue Doppler imaging M-mode: Normal values and association with established echocardiographic and invasive measures of systolic and diastolic function, PLoS One 11 (4) (2016), e0153636.
[4] A.S. Alhakak, R. Møgelvang, P. Schnohr, D. Modin, P. Brainin, G. Gislason, et al., The cardiac isovolumetric contraction time is an independent predictor of incident heart failure in the general population, Int. J. Cardiol. 312 (2020 Aug 1) 81–86.
[5] A.S. Alhakak, P. Brainin, R. Møgelvang, G.B. Jensen, J.S. Jensen, T. Biering-Sørensen, The cardiac isovolumetric contraction time is an independent predictor of incident atrial fibrillation and adverse outcomes following first atrial fibrillation event in the general population, Eur. Heart J. Cardiovasc. Imaging 21 (1) (2020 Jan 1) 49–57.
[6] T. Biering-Sørensen, G. Querejeta Roca, S.M. Hegde, A.M. Shah, B. Claggett, T. H. Mosley, et al., Left ventricular ejection time is an independent predictor of incident heart failure in a community-based cohort, Eur. J. Heart Fail. 20 (7) (2018 Jul) 1106–1114.
[7] A.S. Alhakak, M. Sengeløv, P.G. Jørgensen, N.E. Bruun, C. Johnsen, U. Abildgaard, et al., Left ventricular systolic ejection time is an independent predictor of all-cause mortality in heart failure with reduced ejection fraction, Eur. J. Heart Fail. 23 (2) (2021 Feb) 240–249.
[8] A.S. Alhakak, J.R. Teerlink, J. Lindenfeld, M. Böhm, G.M.C. Rosano, T. Biering-Sørensen, The significance of left ventricular ejection time in heart failure with reduced ejection fraction, Eur. J. Heart Fail. 23 (4) (2021 Apr) 541–551.
[9] A. Haiden, B. Eber, T. Weber, U-shaped relationship of left ventricular ejection time index and all-cause mortality, Am. J. Hypertens. 27 (5) (2014 May) 702–709.
[10] D. Bellavia, P.A. Pellikka, T.P. Abraham, G.B. Al-Zahrani, A. Dispenzieri, J.K. Oh, et al., 'Hypersynchronisation' by tissue velocity imaging in patients with cardiac amyloidosis, Heart Br Card Soc. 95 (3) (2009 Mar) 234–240.
[11] C. Jarnert, M. Edner, H.E. Persson, Prognosis in myocardial infarction patients with heart failure and normal or mildly impaired systolic function, Int. J. Cardiol. 117 (2) (2007 Apr 25) 184–190.
[12] V.G. Florea, M.Y. Henein, M. Cicoira, S.D. Anker, W. Doehner, P. Ponikowski, et al., Echocardiographic determinants of mortality in patients >67 years of age with chronic heart failure, Am. J. Cardiol. 86 (2) (2000 Jul 15) 158–161.
[13] I.J. Lundorff, M. Sengeløv, P. Godsk Jørgensen, S. Pedersen, D. Modin, N. Eske Bruun, et al., Echocardiographic predictors of mortality in women with heart failure with reduced ejection fraction, Circ. Cardiovasc. Imaging. 11 (11) (2018 Nov), e008031.
[14] Bukachi F, Waldenström A, Mörner S, Lindqvist P, Henein MY, Kazzam E. Age dependency in the timing of mitral annular motion in relation to ventricular filling in healthy subjects: Umea general population heart study. Eur. J. Echocardiogr. J. Work Group Echocardiogr. Eur. Soc. Cardiol. 2008 Jul;[1]9(4):522–9.
[15] P. Schnohr, G.B. Jensen, P. Lange, H. Scharling, M. Appleyard, The Copenhagen city heart study. Østerbroundersøgelsen: tables with data from the third examination 1991-1994, Eur. Hear. J. Suppl. 3 (2001) H1–83.
[16] R. Mogelvang, P. Sogaard, S.A. Pedersen, N.T. Olsen, J.L. Marott, P. Schnohr, et al., Cardiac dysfunction assessed by echocardiographic tissue Doppler imaging is an independent predictor of mortality in the general population, Circulation. 119 (20) (2009 May 26) 2679–2685.
[17] K.G. Skaarup, M.C.H. Lassen, J.L. Marott, S.R. Biering-Sørensen, P.G. Jørgensen, M. Appleyard, et al., The impact of cardiovascular risk factors on global longitudinal strain over a decade in the general population: the Copenhagen city heart study, Int. J. Card. Imaging 36 (10) (2020 Oct) 1907–1916.
[18] R.M. Lang, M. Bierig, R.B. Devereux, F.A. Flachskampf, E. Foster, P.A. Pellikka, et al., Recommendations for chamber quantification: a report from the American Society of Echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology, J. Am. Soc. Echocardiogr. Off. Publ. Am. Soc. Echocardiogr. 18 (12) (2005 Dec) 1440–1463.
[19] T. Biering-Sørensen, S.R. Biering-Sørensen, F.J. Olsen, M. Sengeløv, P.G. Jørgensen, R. Mogelvang, et al., Global longitudinal strain by echocardiography predicts long-term risk of cardiovascular morbidity and mortality in a low-risk general population: the Copenhagen City heart study, Circ. Cardiovasc. Imaging. 10 (3) (2017 Mar), e005521.
[20] J. Kjaergaard, C. Hassager, J.K. Oh, J.H. Kristensen, J. Berning, P. Sogaard, Measurement of cardiac time intervals by Doppler tissue M-mode imaging of the anterior mitral leaflet, J. Am. Soc. Echocardiogr. Off. Publ. Am. Soc. Echocardiogr. 18 (10) (2005 Oct) 1058–1065.
[21] T. Biering-Sørensen, R. Mogelvang, S. Pedersen, P. Schnohr, P. Sogaard, J. S. Jensen, Usefulness of the myocardial performance index determined by tissue Doppler imaging m-mode for predicting mortality in the general population, Am. J. Cardiol. 107 (3) (2011 Feb 1) 478–483.
[22] T. Biering-Sørensen, R. Mogelvang, P. Søgaard, S.H. Pedersen, S. Galatius, P. G. Jørgensen, et al., Prognostic value of cardiac time intervals by tissue Doppler imaging M-mode in patients with acute ST-segment-elevation myocardial infarction treated with primary percutaneous coronary intervention, Circ. Cardiovasc. Imaging. 6 (3) (2013 May 1) 457–465.
[23] F. Vancheri, S. Vancheri, M.Y. Henein, Effect of age on left ventricular global Dyssynchrony in asymptomatic individuals: a population study, Echocardiogr. Mt. Kisco. N. 33 (7) (2016 Jul) 977–983.
[24] J.L. Willems, J. Roelandt, H. De Geest, H. Kesteloot, J.V. Joossens, The left ventricular ejection time in elderly subjects, Circulation. 42 (1) (1970 Jul) 37–42.
[25] A. Dodek, J.R. Burg, F.R. Kloster, Systolic time intervals in chronic hypertension: alterations and response to treatment, Chest. 68 (1) (1975 Jul) 51–55.
[26] C.Y. Shim, S. Park, D. Choi, W.I. Yang, I.J. Cho, E.Y. Choi, et al., Sex differences in central hemodynamics and their relationship to left ventricular diastolic function, J. Am. Coll. Cardiol. 57 (10) (2011 Mar 8) 1226–1233.

[27] J.N. Bella, V. Palmieri, D.W. Kitzman, J.E. Liu, A. Oberman, S.C. Hunt, et al., Gender difference in diastolic function in hypertension (the HyperGEN study), Am. J. Cardiol. 89 (9) (2002 May 1) 1052–1056.
[28] S.F. Nagueh, O.A. Smiseth, C.P. Appleton, B.F. Byrd, H. Dokainish, T. Edvardsen, et al., Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, Eur. Heart J. Cardiovasc. Imaging 17 (12) (2016 Dec) 1321–1360.
[29] K. Wierzbowska-Drabik, M. Krzemińska-Pakuła, L. Chrzanowski, M. Plewka, T. Waszyrowski, J. Drozdz, et al., Age-dependency of classic and new parameters of diastolic function, Echocardiogr. Mt. Kisco. N. 25 (2) (2008 Feb) 149–155.
[30] H.A. Feridooni, K.M. Dibb, S.E. Howlett, How cardiomyocyte excitation, calcium release and contraction become altered with age, J. Mol. Cell. Cardiol. 83 (2015 Jun) 62–72.
[31] T. Biering-Sørensen, J.S. Jensen, H.U. Andersen, P. Rossing, M.T. Jensen, Cardiac time intervals and the association with 2D-speckle-tracking, tissue Doppler and conventional echocardiography: the thousand&1 study, Int. J. Card. Imaging 32 (5) (2016 May) 789–798.
[32] P.M. Seferović, W.J. Paulus, Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes, Eur. Heart J. 36 (27) (2015 Jul 14), 1718–27, 1727a–1727c.
[33] A. Yilmaz, K. Yalta, O.O. Turgut, M.B. Yilmaz, A. Erdem, F. Karadas, et al., The effect of smoking on cardiac diastolic parameters including Vp, a more reliable and newer parameter, Cardiol. J. 14 (3) (2007) 281–286.
[34] A. Leone, L. Landini, O. Biadi, A. Balbarini, Smoking and cardiovascular system: cellular features of the damage, Curr. Pharm. Des. 14 (18) (2008) 1771–1777.
[35] R.S. Barua, J.A. Ambrose, L.J. Eales-Reynolds, M.C. DeVoe, J.G. Zervas, D.C. Saha, Heavy and light cigarette smokers have similar dysfunction of endothelial vasoregulatory activity: an in vivo and in vitro correlation, J. Am. Coll. Cardiol. 39 (11) (2002 Jun 5) 1758–1763.
[36] G.C. Kane, B.L. Karon, D.W. Mahoney, M.M. Redfield, V.L. Roger, J.C. Burnett, et al., Progression of left ventricular diastolic dysfunction and risk of heart failure, JAMA. 306 (8) (2011 Aug 24) 856–863.
[37] D.A. Kass, J.G.F. Bronzwaer, W.J. Paulus, What mechanisms underlie diastolic dysfunction in heart failure? Circ. Res. 94 (12) (2004 Jun 25) 1533–1542.
[38] M.A. Pfeffer, A.M. Shah, B.A. Borlaug, Heart failure with preserved ejection fraction in perspective, Circ. Res. 124 (11) (2019 May 24) 1598–1617.
[39] F. Aziz, L.A. Tk, C. Enweluzo, S. Dutta, M. Zaeem, Diastolic heart failure: a concise review, J. Clin. Med. Res. 5 (5) (2013 Oct) 327–334.
[40] S.A. Hunt, W.T. Abraham, M.H. Chin, A.M. Feldman, G.S. Francis, T.G. Ganiats, et al., 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and Management of Heart Failure in adults: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation, Circulation. 119 (14) (2009 Apr 14) e391–e479.
[41] G.A. Roth, G.A. Mensah, C.O. Johnson, G. Addolorato, E. Ammirati, L.M. Baddour, et al., Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study, J. Am. Coll. Cardiol. 76 (25) (2020 Dec 22) 2982–3021.
[42] E. Vittinghoff, C.E. McCulloch, Relaxing the rule of ten events per variable in logistic and cox regression, Am. J. Epidemiol. 165 (6) (2007 Mar 15) 710–718.
[43] J. Sundbøll, K. Adelborg, T. Munch, T. Frøslev, H.T. Sørensen, H.E. Bøtker, et al., Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study, BMJ Open 6 (11) (2016 Nov 18), e012832.
[44] S.K. Thygesen, C.F. Christiansen, S. Christensen, T.L. Lash, H.T. Sørensen, The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of patients, BMC Med. Res. Methodol. 11 (2011 May 28) 83.