ORIGINAL RESEARCH

Cardiac Time Intervals Measured by Tissue Doppler Imaging M-mode: Association With Hypertension, Left Ventricular Geometry, and Future Ischemic Cardiovascular Diseases

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***Background*—**We hypothesized that the cardiac time intervals reveal reduced myocardial function in persons with hypertension and are strong predictors of future ischemic cardiovascular diseases in the general population.

***Methods and Results*—**In a large community-based population study, cardiac function was evaluated in 1915 participants by using both conventional echocardiography and tissue Doppler imaging (TDI). The cardiac time intervals, including the isovolumic relaxation time (IVRT), isovolumic contraction time (IVCT), and ejection time (ET), were obtained by TDI M-mode through the mitral leaflet. IVCT/ET, IVRT/ET, and myocardial performance index [MPI=(IVRT+IVCT)/ET] were calculated. After multivariable adjustment for clinical variables the IVRT, IVRT/ET, and MPI, remained significantly impaired in persons with hypertension (n=826) compared with participants without hypertension (n=1082). Additionally, they displayed a significant dose–response relationship, between increasing severity of elevated blood pressure and increasing left ventricular mass index ($P<0.001$ for all). Further, during follow-up of a median of 10.7 years, 435 had an ischemic cardiovascular disease (ischemic heart disease, peripheral arterial disease, or stroke). The IVRT/ET and MPI were powerful and independent predictors of future cardiovascular disease, especially in participants with known hypertension. They provide prognostic information incremental to clinical variables from the Framingham Risk Score, the SCORE risk chart, and the European Society of Hypertension/European Society of Cardiology risk chart.

***Conclusion*—**The cardiac time intervals identify impaired cardiac function in individuals with hypertension, not only independent of conventional risk factors but also in participants with a normal conventional echocardiographic examination. The IVRT/ET and MPI are independent predictors of future cardiovascular disease especially in participants with known hypertension. **(*J Am Heart Assoc*. 2016;5:e002687 doi: 10.1161/JAHA.115.002687)**

Key Words: cardiac time intervals • hypertension • ischemic cardiovascular disease • risk-stratification • tissue Doppler imaging

Hypertension is common in the general population; the prevalence is reported to be ≈30% to 45%.[1] Increasing blood pressure (BP) and hypertension are strong predictors of future ischemic cardiovascular diseases (ICVDs) such as stroke, ischemic heart disease (IHD), and peripheral artery disease (PAD).[2–4] The risk of ICVD increases continuously with increasing BP without any evidence of a lower threshold.[5] In addition, the presence of elevated BP leads to organ damage in the heart, eyes, blood vessels, kidneys, and brain, all of which often is asymptomatic.[1] Asymptomatic organ damage is an intermediate in the continuum from elevated BP to fulminant ICVD. When asymptomatic organ damage of the heart has occurred, the progression to fulminant ICVD is imminent, explaining the increased risk of ICVD with the observation of asymptomatic organ damage.[1,6–8] Increased BP and hypertension leads to specific changes in the heart characterized by left ventricular (LV) hypertrophy (LVH) and diastolic dysfunction.[1,9,10] Including echocardiography in the risk stratification of patients with hypertension has been demonstrated to be valuable[6,11,12]; however, echocardiography is not recommended as a part of the first line of the diagnostic workup in patients with hypertension.[1] Nevertheless, because the risk of ICVD increases continuously with increasing BP[5] and LVH,[7,8] the optimal echocardiographic marker for risk stratification in hypertension-related diseases should be able to display

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An accompanying Table S1 is available at http://jaha.ahajournals.org/content/5/1/e002687/suppl/DC1

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changes in both severity of elevated BP and LV geometry, improve the current risk prediction models, and identify early cardiac impairment before the development of asymptomatic organ damage of the heart.

The cardiac time intervals are sensitive markers of cardiac dysfunction, even when it goes unrecognized by conventional echocardiography,[13–15] and they have previously been demonstrated to contain prognostic information incremental to the conventional echocardiographic parameters in various populations.[16–19] A novel method of obtaining the global cardiac time intervals has recently evolved. With use of this method, the cardiac time intervals are obtained by evaluating the mitral valve movement through the cardiac cycle with simple color TDI M-mode analysis.[19–22]

However, it is unknown if the cardiac time intervals are able to identify miniscule cardiac impairments in individuals with hypertension, which are unrecognized by conventional echocardiography, and if these time intervals are affected according to BP severity and LV geometry. Further, it is unknown if these cardiac time intervals can be used to predict hypertension-related diseases such as ICVDs.

Methods

Study Population

Within the Copenhagen City Heart Study, a longitudinal cohort study of cardiovascular disease and risk factors, an echocardiographic substudy was performed.[22–25] The present study includes all participants from the fourth Copenhagen City Heart Study examination 2001–2003 who had an echocardiographic examination, including TDI, performed (Figure 1). We hereby obtained cardiac time intervals from 1915 participants aged 20 to 93 years. Participants in whom time intervals were unmeasurable were caused by the trigger point not being placed at the QRS complex or the TDI image not including the whole cardiac cycle. The present study only included participants in whom all the cardiac time intervals were measurable. Whether a participant underwent echocardiography as part of the fourth Copenhagen City Heart Study examination was independent of his or her health status and other risk factors (Figure 1).

All participants gave written informed consent, and the study was performed in accordance with the second Helsinki Declaration and approved by the regional ethics committee.

Health Examination

All participants answered a self-administered questionnaire and underwent thorough physical examinations. BP of all participants was measured with the London School of Hygiene

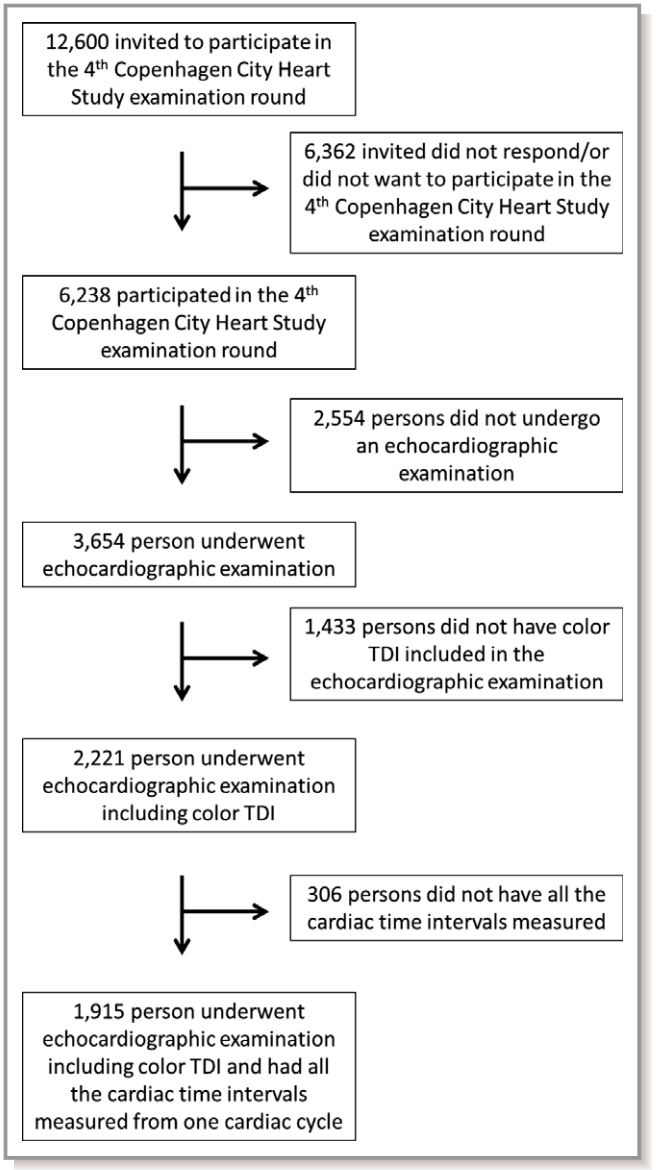

Figure 1. Flow diagram of the study population. TDI indicates tissue Doppler imaging.

sphygmomanometer. Hypertension was defined as systolic BP (SBP) of ≥140 mm Hg, diastolic BP (DBP) of ≥90 mm Hg, or use of antihypertensive medication.[26] A 12-lead ECG was recorded at rest in a supine position and coded according to the Minnesota code. Plasma cholesterol and blood glucose values were measured on nonfasting venous blood samples.[27] Diabetes mellitus was defined as plasma glucose concentration of ≥11.1 mmol/L, use of insulin or other antidiabetic medicine, self-reported disease, or hemoglobin A1c level of ≥7.0%.[28,29] Previous IHD was defined as a history of hospital admission for acute coronary artery occlusion, percutaneous coronary intervention or coronary artery bypass graft surgery, or major ischemic alterations on the ECG as defined by Minnesota codes 1.1 to 3.

Echocardiography

All echocardiograms were obtained by 3 sonographers with the use of Vivid 5 ultrasound systems (GE Healthcare) with a 2.5-MHz transducer. All participants were examined with conventional 2-dimensional echocardiography and color TDI. All echocardiograms were stored on magneto-optical discs and an external FireWire hard drive and analyzed offline with commercially available software (EchoPac; GE Medical) by 2 investigators (T.B.S. and R.M.), who were blinded to all other information.

Conventional echocardiography

Regional function was evaluated by the 16 standard segments model, as suggested by the American Society of Echocardiography.[9] LV ejection fraction (LVEF) was evaluated by 1 observer on the basis of the wall motion index score.[30] LV systolic dysfunction was defined as LVEF <50%.[23–25]

An M-mode still frame between the tips of the mitral leaflets and the tips of the papillary muscles was recorded in the parasternal long-axis view. If the correct 90° angle to the long axis of the ventricle could not be obtained, 2-dimensional images were used instead to quantify the myocardial thickness and the dimensions of the LV in end diastole (LVIDd) and the left atrium in end-systole (LAd). LV mass index (LVMI) was calculated as the anatomic mass[9] divided by body surface area.[31] Pulsed-wave Doppler at the apical view was used to record mitral inflow between the tips of the mitral leaflets. Peak velocity of early (E) and atrial (A) diastolic filling and deceleration time of the E-wave were measured, and the E/A ratio was calculated. LV hypertrophy (LVH) was defined as LVMI ≥96 g/m^2 for women and ≥116 g/m^2 for men.[9] LV dilatation was considered present if LVIDd/height ≥3.3 cm/m.[9]

Diastolic dysfunction was defined as deceleration time <140 ms and $E/A_{<50\ years}$ >2.5, $E/A_{50–70\ years}$ >2, or $E/A_{>70\ years}$ >1.5.[25]

Participants were stratified according to LV geometry. Normal geometry was defined as a relative wall thickness (RWT) ≤0.42 and absence of LVH; concentric remodeling was defined as an RWT >0.42 and absence of LVH; eccentric hypertrophy was defined as an RWT ≤0.42 and the presence of LVH; and concentric hypertrophy was defined as an RWT >0.42 and the presence of LVH.[9]

A normal conventional echocardiographic examination was defined as the absence of LVH, dilatation, LVEF <50%, and diastolic dysfunction.[25]

Tissue Doppler imaging

Color TDI tracings were obtained with the range gate placed at the septal and lateral mitral annulus in the 4-chamber view.

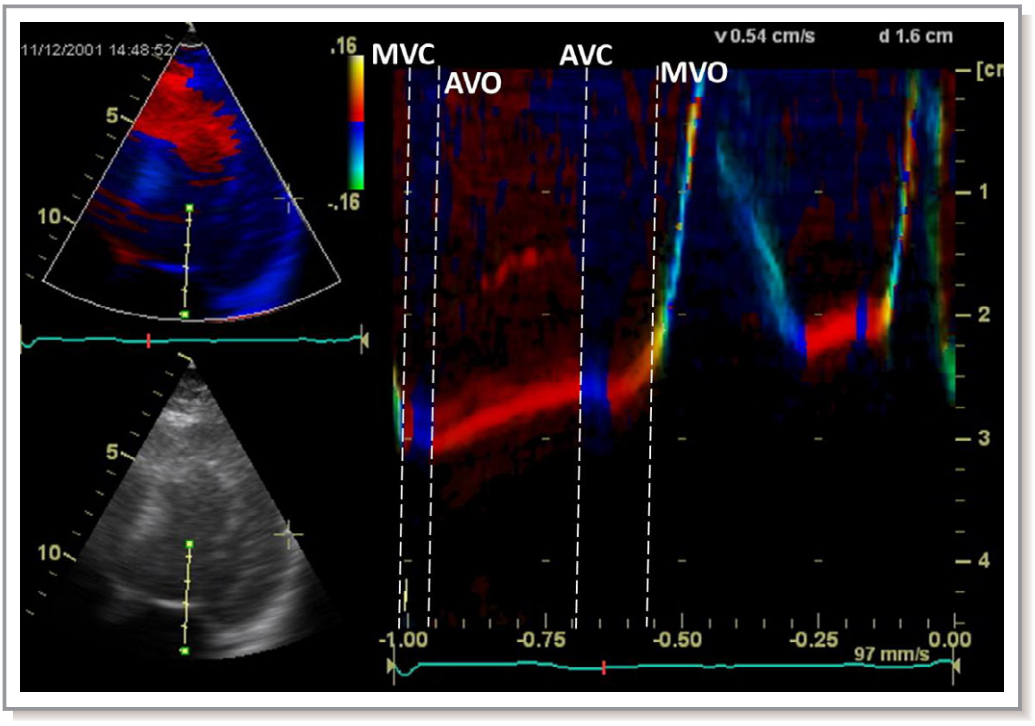

Figure 2. The cardiac time intervals assessed by a color tissue Doppler imaging (TDI) M-mode line through the mitral leaflet. Left: Four-chamber gray-scale (bottom) and color TDI (top) views in end systole displaying the position of the M-mode line used for measuring the cardiac time intervals. Right: Color diagram of the TDI M-mode line through the mitral leaflet. AVC indicates aortic valve closure; AVO, aortic valve opening; MV, mitral valve; MVC, MV closing; MVO, MV opening.

The peak longitudinal early diastolic (e') velocity was measured, and the average was calculated from the lateral and septal velocities and used to obtain the E/e'.

With placement of a 2- to 4-cm straight M-mode line through the septal half of the mitral leaflet in the color TDI 4-chamber view, the cardiac time intervals were measured directly from the color diagram[19,22] (Figure 2). The IVCT was defined as the time interval from the mitral valve closure, determined by the color shift from blue/turquoise to red at end diastole, to the aortic valve opening determined by the color shift from blue to red (Figure 2). The ET was defined as the time interval from aortic valve opening to aortic valve closing, determined by the color shift from red to blue at end systole (Figure 2). The IVRT was defined as the time interval from the aortic valve closing to the mitral valve opening, determined by the color shift from red-orange to yellow (Figure 2). The method has previously been validated[19,21,22] and demonstrated to be superior to the conventional method of obtaining the cardiac time intervals.[21,22] Further, we have previously demonstrated high reproducibility of the method in this population.[22] Both isovolumic time intervals were divided by ET, creating IVRT/ET and IVCT/ET, respectively, and MPI was calculated as the sum of the 2 [(IVRT+IVCT)/ET].

Follow-up and Outcome

The primary end point of ICVD was the combined end point of being admitted with IHD, PAD, or stroke. Follow-up was 100%. Follow-up data on admission with IHD, PAD, or stroke were obtained from the Danish National Board of Health's National Patient Registry, with the use of *International Classification of Diseases, 10th Edition* codes DG45 to DG459, DI20 to DI259, DI608 to DI749, I213 to I258, and I613 to I713.

Statistics

Proportions were compared by using χ^2 test, continuous Gaussian distributed variables with Student *t* test and Mann–Whitney test if non–Gaussian distributed. The association between the cardiac time intervals and hypertension was tested by univariable and multivariable regression analyses including significant confounders detected from the baseline differences between participants with and those without hypertension (Table). Participants with missing data in either of the variables included in multivariable models were excluded from the analysis. Imputing of missing data was not performed in the present report. Linearity, variance homogeneity, and the assumption of normality were tested with plots of residuals. Trends were analyzed by linear regression analyses, and departure from linearity was assessed by simultaneous assessment of linear and quadratic effects. Cumulative incidence curves of future major adverse cardiac events were obtained by competing risk Cox proportional hazards regression models. Subdistribution hazard ratios (SHRs) were calculated by competing risk Cox proportional hazards regression analyses. The assumptions of proportional hazards in the models were tested graphically and tested based on the Schoenfeld residuals.

Table. Population Characteristics

	Nonhypertensive (n=1082)	Hypertension (n=826)	*P* Value
Age, y	51±15	68±11	<0.001
Male sex, n	44% (473)	41% (337)	0.20
Systolic blood pressure, mm Hg	120±12	156±18	<0.001
Diastolic blood pressure, mm Hg	73±9	85±12	<0.001
Heart rate, beats per minute	65±11	70±12	<0.001
Smoking status			
Never, n	35% (372)	32% (261)	
Previous, n	31% (339)	36% (296)	0.10
Current, n	34% (366)	32% (261)	
Diabetes, n	7% (75)	15% (124)	<0.001
Cholesterol, mmol/L	5.3±1.1	5.8±1.1	<0.001
Previous ischemic heart disease, n	3% (30)	10% (80)	<0.001
Previous ischemic stroke, n	1% (6)	4% (29)	<0.001
BMI, kg/m^2	24.5±3.4	26.6±4.2	<0.001
eGFR, mL/min per 1.73 m^2	79.2±15.7	72.4±16.1	<0.001
Atrial fibrillation/flutter, n	1% (12)	3% (23)	0.007
LVEF <50%, n	1% (5)	2% (13)	0.012
LV dilatation, n	4% (38)	6% (41)	0.037
LV hypertrophy, n	9% (85)	29% (194)	<0.001
LV diastolic dysfunction, n	1% (5)	2% (15)	0.003
No. of ICVD events during follow-up	13% (136)	36% (297)	<0.001
Cardiac time intervals			
IVRT, ms	94±21	110±24	<0.001
IVCT, ms	36±13	39±15	<0.001
ET, ms	286±24	281±30	<0.001
IVRT/ET	0.33±0.08	0.40±0.11	<0.001
IVCT/ET	0.13±0.05	0.14±0.06	<0.001
MPI	0.46±0.11	0.54±0.15	<0.001

BMI indicates body mass index; eGFR, estimated glomerular filtration rate; ET, ejection time; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; LV, left ventricle; LVEF, left ventricular ejection fraction; MPI, myocardial performance index.

Models were constructed that used logistic regression models and predicted the risk of future hypertension-related ICVDs for participants followed for a median of 10.7 years. Reclassification analyses that used risk categories of 0% to 5%, 5% to 10%, 10% to 20%, and >20% for low-, intermediate-, high-, and very high-risk categories,[1] respectively, in accordance with the Framingham Risk Score categories,[32] were used to assess the net reclassification improvement[33] when adding the IVRT/ET, the MPI, LVEF, and diastolic dysfunction to the significant clinical predictors from the Framingham Risk Score,[32] the Systemic Coronary Evaluation (SCORE) risk chart,[34] and the European Society of Hypertension/European Society of Cardiology (ESH/ESC) risk chart.[1] Non–Gaussian distributed continuous variables (LVMI and E/e') were categorized into quartiles when included as confounders in the models. A *P*-value ≤0.05 in 2-sided test was considered statistically significant. All analyses were performed with STATA Statistics/Data analysis, SE 12.0 (StataCorp).

Results

Cardiac Time Intervals and Hypertension

Participants with hypertension displayed impaired systolic and diastolic function as determined by affected systolic and diastolic cardiac time intervals (Table). After multivariable adjustment for clinical variables, the IVRT, the IVCT, and the combined indexes including information about systolic and diastolic function, the IVRT/ET, and the MPI, remained independently impaired in participants with hypertension (Figure 3). However, the IVCT did not remain significantly impaired in participants with hypertension when the analysis was confined to persons with a normal conventional echocardiographic examination (Figure 3). In contrast, the IVRT, IVRT/ET, and MPI remained significantly impaired after multivariable adjustment when the analysis was confined to persons with a normal conventional echocardiographic examination (Figure 3).

Cardiac Time Intervals and Elevated BP

To investigate if cardiac dysfunction as assessed by cardiac time intervals was associated to severity of elevated BP, our study population was stratified into 4 groups according to BP: normal, high normal, hypertension stage 1, and hypertension stage 2 (Figure 4). The IVRT and the combined indexes, including information about systolic and diastolic function, the IVRT/ET, and the MPI, increased incrementally with increasing severity of elevated BP (Figure 4). This pattern of incremental increase with increasing severity of elevated BP remained statistically significant after multivariable adjustment for both clinical variables and conventional echocardiographic parameters (Figure 4). The same incremental pattern was found when stratifying the participants according to the tertiles of the mean arterial BP (Figure 5). To determine if the cardiac time intervals can detect miniscule cardiac dysfunction preceding fulminant hypertension, we confined the analysis to participants without hypertension and found that the IVRT, IVRT/ET, and MPI were significantly higher in participants with high-normal BP than in the group with normal BP (normal versus prehypertensive: IVRT, 88 ms [95% CI 87–90 ms] versus 98 ms [95% CI 97–100 ms], *P*<0.001; IVRT/ET, 0.31 [95% CI 0.30–0.31] versus 0.35 [95% CI 0.34–0.36], *P*<0.001; MPI, 0.43 [95% CI 0.42–0.44] versus 0.48 [95% CI 0.47–0.49], *P*<0.001).

Cardiac Time Intervals and LV Geometry

All the cardiac time intervals displayed impaired cardiac function with increasing values of the IVRT, IVCT, IVRT/ET, IVCT/ET, and MPI (β-coefficients: IVRT, 2.15 ms; IVCT, 1.23 ms; IVRT/ET, 0.01; IVCT/ET, 0.01; MPI, 0.02) and decreasing value of the ET (β-coefficient: ET, −1.68) for increasing LVMI (per. 10 g/m^2 increase) (*P*<0.001 for all) (Figure 5). This pattern remained statistically significant for all the cardiac time intervals even after multivariable adjustment for age, sex, body mass index, estimated glomerular filtration rate, heart rate, SBP, DBP, diabetes, cholesterol, atrial fibrillation, IHD, ischemic stroke, LVEF <50%, LVIDd, LAd, deceleration time, E/A ratio <1, and E/e' (*P*<0.05 for all). All the cardiac time intervals, except IVCT, displayed the same pattern with increasing values of the IVRT, IVRT/ET, IVCT/ET, and MPI (β-coefficients: IVRT, 5.743 ms; IVRT/ET, 0.025; IVCT/ET, 0.004; MPI, 0.029) and decreasing value of the ET (β-coefficient: ET, −3.733 ms) for increasing RWT (pr. 10% increase) (*P*<0.02 for all). This pattern also remained statistically significant for all the cardiac time intervals, except for the IVRT, after multivariable adjustment for the same variables as listed earlier (*P*<0.05 for all).

Participants were divided into 4 groups according to their LV geometry (Figure 6). Only the IVRT, IVRT/ET, and MPI displayed impaired cardiac function in all the pathological LV geometry groups (concentric remodeling, concentric hypertrophy, and eccentric hypertrophy) compared with participants with normal geometry (*P*<0.001 for all) (Figure 6). After multivariable adjustment for age, sex, body mass index, estimated glomerular filtration rate, heart rate, hypertension, SBP, DBP, diabetes, cholesterol, atrial fibrillation, IHD, ischemic stroke, LVEF <50%, LVIDd, LAd, deceleration time, E/A ratio <1, and E/e', only the combined indexes including information about systolic and diastolic function, the IVRT/ET, and the MPI, remained statistically significantly impaired in all the pathological LV geometry groups (Figure 6).

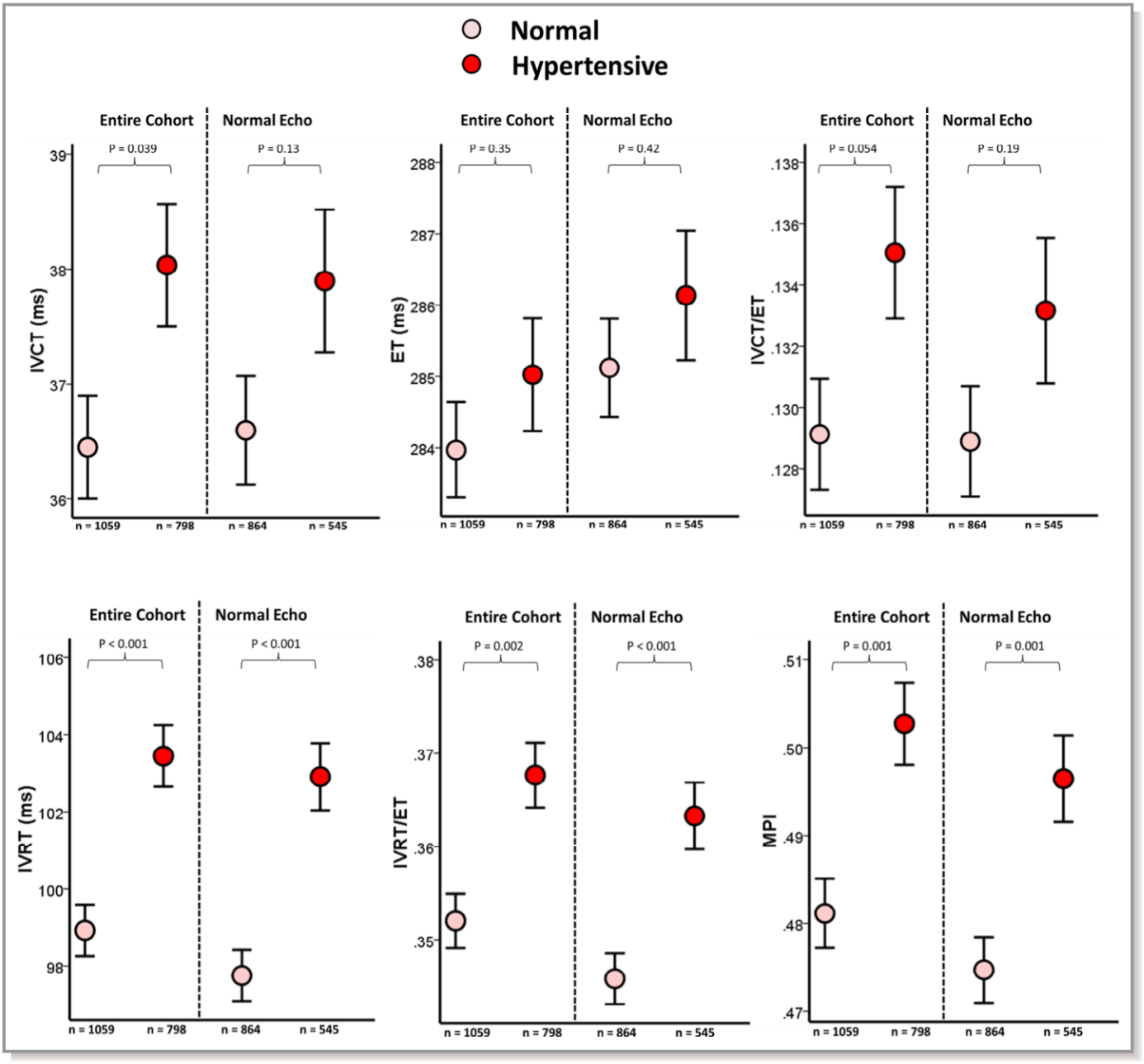

Figure 3. Systolic and diastolic function determined by the cardiac time intervals in participants with and without hypertension after multivariable adjustment. Multivariable adjusted means are depicted for the cardiac time intervals in participants with and without hypertension for both the entire study cohort and the subgroup with a normal conventional echocardiographic examination. Multivariable adjustment designates adjustment for age, sex, body mass index, estimated glomerular filtration rate, heart rate, diabetes, cholesterol, atrial fibrillation, ischemic heart disease and previous ischemic stroke. Normal echo designates the absence of left ventricular hypertrophy, dilatation and ejection fraction <50%, and severe diastolic dysfunction.[25] Bars indicate SE. ET indicates ejection time; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; MPI, myocardial performance index.

Usefulness of the Cardiac Time Intervals to Predict ICVDs

During follow-up of median 10.7 (IQR 7.3–11.1) years, 435 participants reached the combined end point of ICVD (IHD, stroke, or PAD). In univariable analysis, all the cardiac time intervals were significant predictors of future ICVDs (P<0.001) (Table S1 and Figures 7 and 8A). After multivariable adjustment for age, sex, body mass index, estimated glomerular filtration rate, heart rate, hypertension, SBP, DBP, diabetes, cholesterol, smoking status, atrial fibrillation, IHD, ischemic stroke, LVEF <50%, diastolic dysfunction, and LVH, only the combined indexes including information about systolic and diastolic function, the IVRT/ET, and the MPI remained

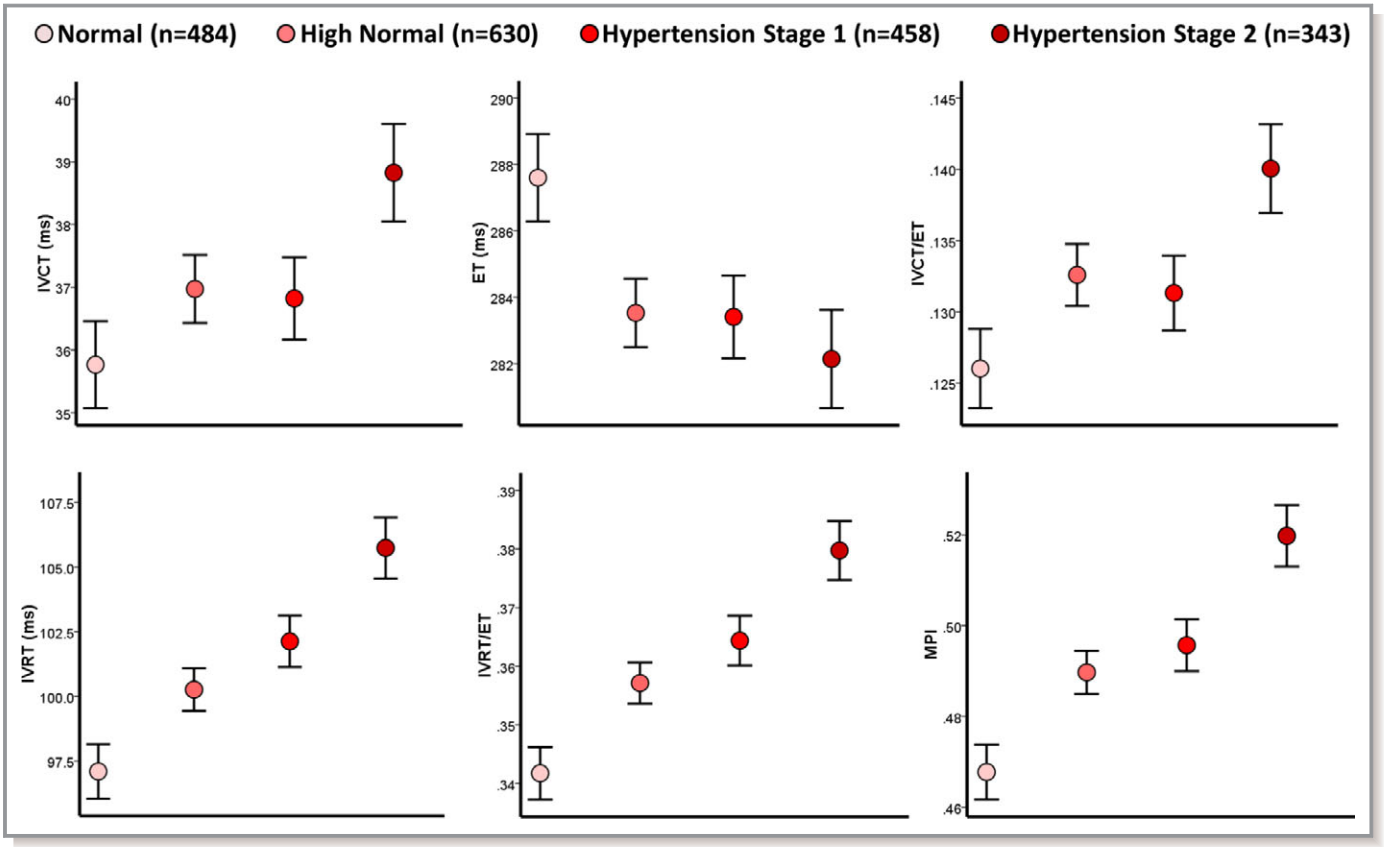

Figure 4. Systolic and diastolic function determined by the cardiac time intervals according to elevated blood pressure severity. Depicting the adjusted means of the cardiac time intervals in participants stratified according to blood pressure, after adjustment for age and sex. The study population was divided into 4 groups according to blood pressure: normal (<120/80 mm Hg), high normal (between 120/80 and 140/90 mm Hg), stage 1 hypertension (between 140/90 and 160/100 mm Hg), and stage 2 hypertension (≥160/100 mm Hg). The pattern of incremental increase of the IVRT, IVRT/ET, and MPI with increasing severity of elevated blood pressure, remained statistically significant after multivariable adjustment for age, sex, body mass index, estimated glomerular filtration rate, heart rate, diabetes, cholesterol, atrial fibrillation, ischemic heart disease, ischemich stroke, left ventricular ejection fraction <50%, left ventricular dimension in end diastole, left atrium diameter in end systole, left ventricular mass index, deceleration time of early diastolic inflow, peak transmitral early diastolic inflow velocity/peak transmitral late diastolic inflow velocity ratio <1, and E/e'. Bars indicate SE. ET indicates ejection time; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; MPI, myocardial performance index.

independent predictors of future ICVDs (IVRT/ET: SHR, 1.11 [95% CI 1.00–1.23] per 0.1 increase, *P*=0.050; MPI: SHR, 1.11 [95% CI1.01–1.21] per 0.1 increase, *P*=0.024) (Figure 8C). When confining the analysis to only include participants with no previous history of IHD, IVRT/ET only remained borderline significant, whereas MPI remained an independent predictor of ICVDs (IVRT/ET: SHR, 1.10 [95% CI 0.99–1.22] per 0.1 increase, *P*=0.084; MPI: SHR, 1.10 [95% CI 1.00–1.21] per 0.1 increase, *P*=0.047). Hypertension significantly modified the relationship between IVRT, IVRT/ET, MPI, and ICVD (*P* for interaction: *P*≤0.001 for all). The IVRT, IVRT/ET, and MPI primarily predicted ICVD in participants with hypertension but not in participants without hypertension (Figure 8D). Further, only the MPI remained an independent predictor of ICVD in participants with hypertension (MPI: SHR, 1.12 [95% CI 1.01–1.23] per 0.1 increase, *P*=0.027) (Figure 8D). In addition, reclassification analysis demonstrated that adding IVRT/ET or MPI to the clinical predictors from the Framingham Risk Score[32] and the SCORE risk chart[34] (age, sex, cholesterol, smoking status, and SBP) yielded better predicting models with significant increase in the categorical net reclassification improvement of 0.0227 (95% CI 0.0017–0.0437, *P*=0.034) for IVRT/ET and 0.402 (95% CI 0.0150–0.0653, *P*=0.002) for the MPI, respectively. Additionally, reclassification analysis demonstrated that adding IVRT/ET or MPI to a model including the clinical predictors from the newer ESH/ESC risk chart[1] (age, sex, smoking status, cholesterol, diabetes, SBP, DBP, LVH, chronic kidney disease [defined as estimated glomerular filtration rate ≤60 mL/min per 1.73 m^2], IHD, and ischemic stroke) yielded better predicting models with significant increase in the categorical net reclassification improvement of 0.0341 (95% CI 0.0079–0.0603, *P*=0.011) for IVRT/ET and 0.344 (95% CI 0.0039–0.0648, *P*=0.027) for the MPI, respectively. In contrast, when

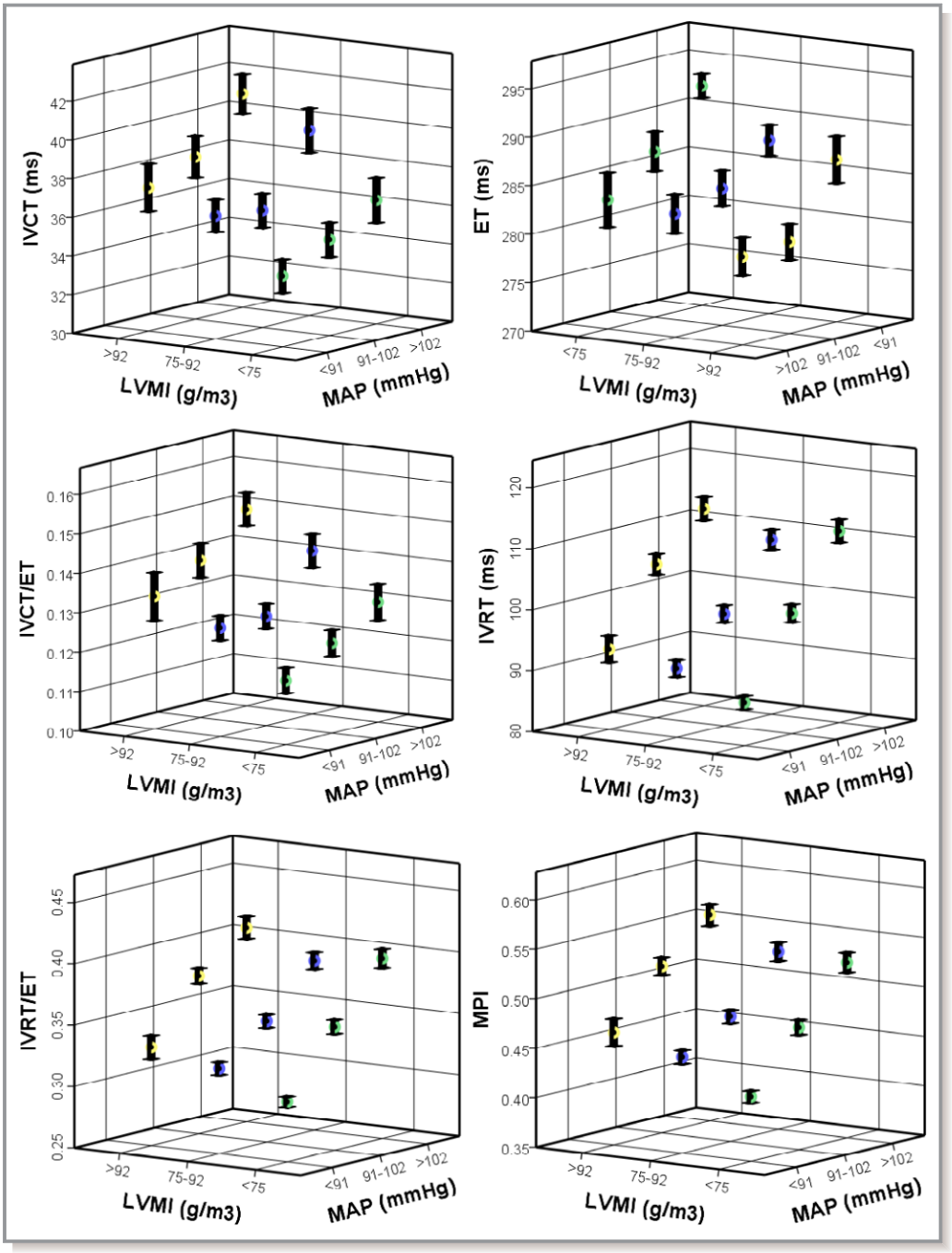

Figure 5. The association between the cardiac time intervals and LVMI and MAP. The association between the cardiac time intervals and the LVMI and MAP. Participants were stratified into tertiles of the LVMI and MAP. Bars indicate SE. ET indicates ejection time; IVRT, isovolumic relaxation time; LVMI, left ventricular mass index; MAP, mean arterial blood pressure; MPI, myocardial performance index.

adding LVEF or diastolic dysfunction to either of the aforementioned models, the predicting models did not improve. When added to the clinical predictors from the Framingham Risk Score[32] and the SCORE risk chart,[34] *P* for LVEF=0.62 and *P* for diastolic dysfunction=0.82; when added to the clinical predictors from the newer ESH/ESC risk chart,[1] *P* for LVEF=0.90 and *P* for diastolic dysfunction=0.12.

Discussion

In the largest prospective study to date of a random sample of participants from the general population undergoing comprehensive echocardiography including an assessment of the cardiac time intervals by TDI M-mode, we found that (1) the cardiac time intervals (IVRT, IVRT/ET, and MPI) display

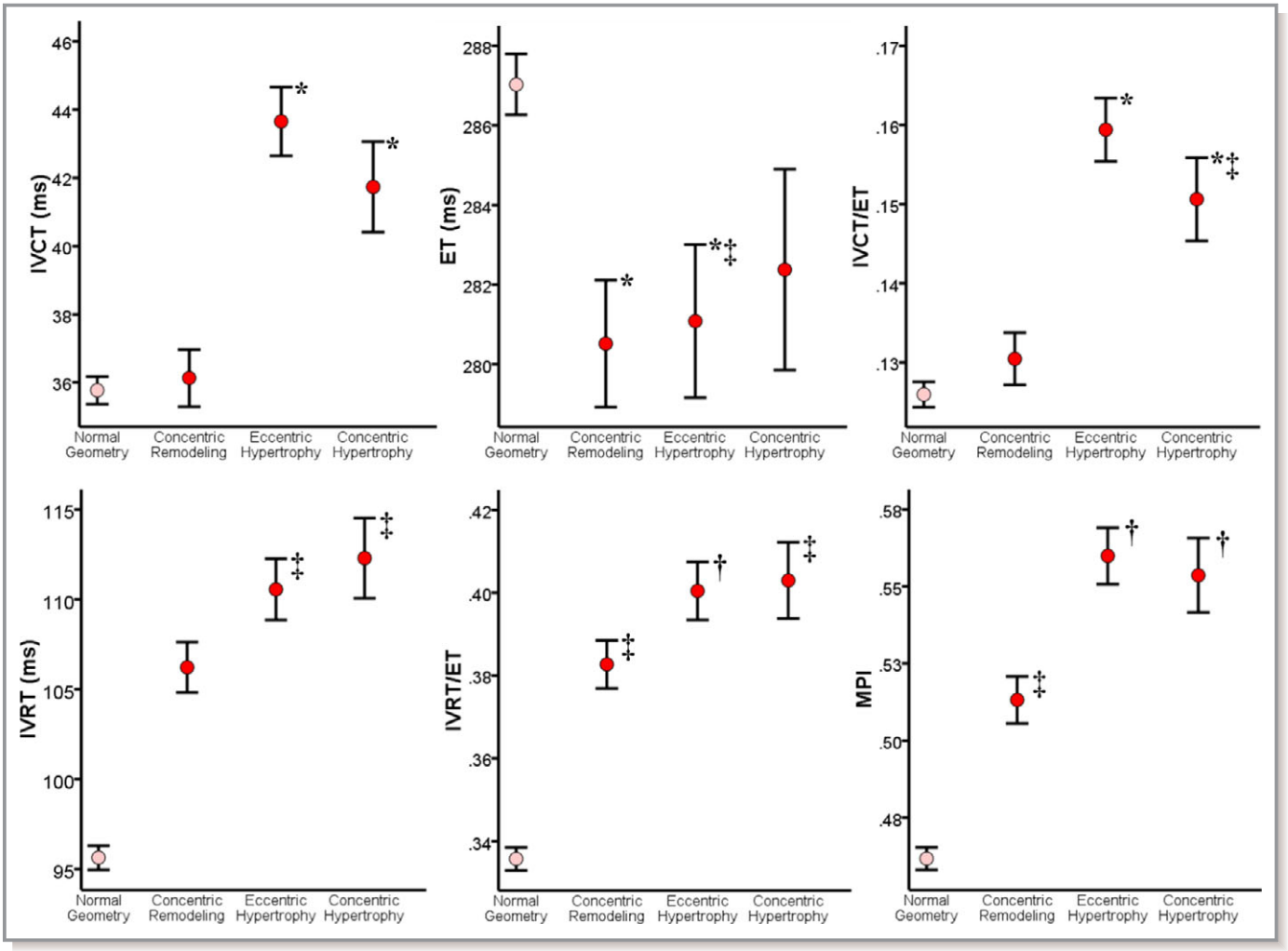

Figure 6. The cardiac time intervals in participants with normal left ventricular geometry (n=1122), concentric remodeling (n=259), eccentric hypertrophy (n=177), and concentric hypertrophy (n=103). Cardiac time intervals are depicted in participants with normal left ventricular geometry and pathological left ventricular geometry. Displays mean and SEs. *Significant difference ($P<0.01$) when comparing the participants with normal left ventricular geometry to participants with pathological left ventricular geometry. †$P\leq0.01$ and ‡$P\leq0.05$ after adjustment for age, sex, body mass index, estimated glomerular filtration rate, heart rate, hypertension, systolic and diastolic blood pressures, diabetes, cholesterol, atrial fibrillation, ischemic heart disease, previous ischemic stroke, left ventricular ejection fraction <50%, left ventricular dimension in end diastole, left atrial diameter, deceleration time of early diastolic inflow, peak transmitral early diastolic inflow velocity/peak transmitral late diastolic inflow velocity ratio <1, and E/e', when comparing the participants with normal left ventricular geometry to participants with pathological left ventricular geometry. ET indicates ejection time; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; MPI, myocardial performance index.

impaired cardiac function in individuals with hypertension, not only independent of conventional risk factors but also in participants with a normal conventional echocardiographic examination; (2) a significant dose–response relationship exists between increasing severity of BP and incremental impairment in cardiac function determined by the cardiac time intervals (IVRT, IVRT/ET, and MPI); (3) the combined indexes encompassing information on both systolic and diastolic function (the IVRT/ET and the MPI) independently display cardiac dysfunction in all types of pathological LV geometry; (4) the IVRT/ET and the MPI are independent predictors of future ICVDs, even after adjustment for conventional echocardiographic parameters, but they primarily provide prognostic information regarding the risk of future ICVD in participants with hypertension; and (5) the IVRT/ET and the MPI improve the predictive models for future ICVDs when added to the Framingham Risk Score, the SCORE risk chart, and the ESH/ESC risk chart.

Cardiac Time Intervals, Hypertension, and LV Geometry

Cardiac function was significantly impaired in participants with hypertension compared with participants with normal

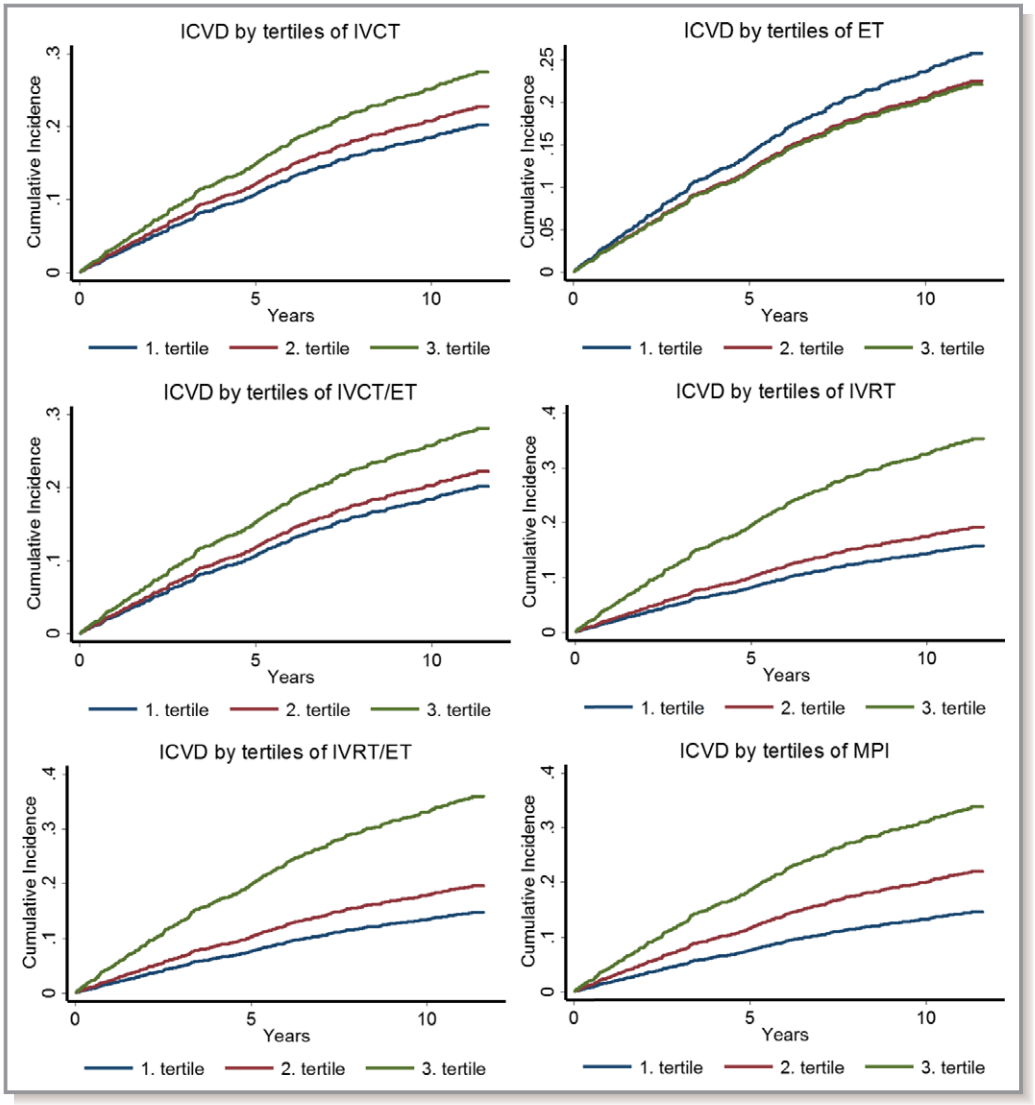

Figure 7. The cardiac time intervals and risk of future ischemic cardiovascular disease. Depicting the cumulative incidence of ICVD for participants stratified according to the tertiles of IVCT (1. tertile <30 ms; 2. tertile ≥30 ms to <40 ms; 3. tertile ≥40 ms), IVRT (1. tertile <90 ms; 2. tertile ≥90 ms to <109 ms; 3. tertile ≥109 ms), ET (1. tertile <275 ms; 2. tertile ≥275 ms to <296 ms; 3. tertile ≥296 ms), IVCT/ET (1. tertile <0.10; 2. tertile ≥0.10–<0.14; 3. tertile ≥0.14), IVRT/ET (1. tertile <0.31; 2. tertile ≥0.31–<0.39; 3. tertile ≥0.39) and MPI (1. tertile <0.43; 2. tertile ≥0.43–<0.52; 3. tertile ≥0.52). ET indicates ejection time; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; MPI, myocardial performance index.

BP, determined by affected systolic and diastolic cardiac time intervals (Table). However, after multivariable adjustment, and when confining the analysis to participants with a normal conventional echocardiographic examination, only IVRT, IVRT/ET, and MPI remained significantly impaired in participants with hypertension (Figure 3). These results were expected, because it is well known that patients with hypertension primarily have an impaired diastolic function and not an impaired systolic function,[35,36] which is in accordance with our results where only the time intervals containing information about the diastolic function remained impaired after multivariable adjustment.

However, the pivotal finding in Figure 3 was that the cardiac time intervals were capable of identifying subtle impairments in the cardiac function in participants with hypertension, which were unnoticed with the use of conventional echocardiography (Figure 3). Therefore, the cardiac time intervals, containing information about diastolic function, seem capable of identifying participants at risk of hypertension-related asymptomatic organ damage of the heart, despite of normal conventional echocardiography.

In accord with our results, a previous small-scale study with 62 hypertensive patients and 15 controls also found IVRT

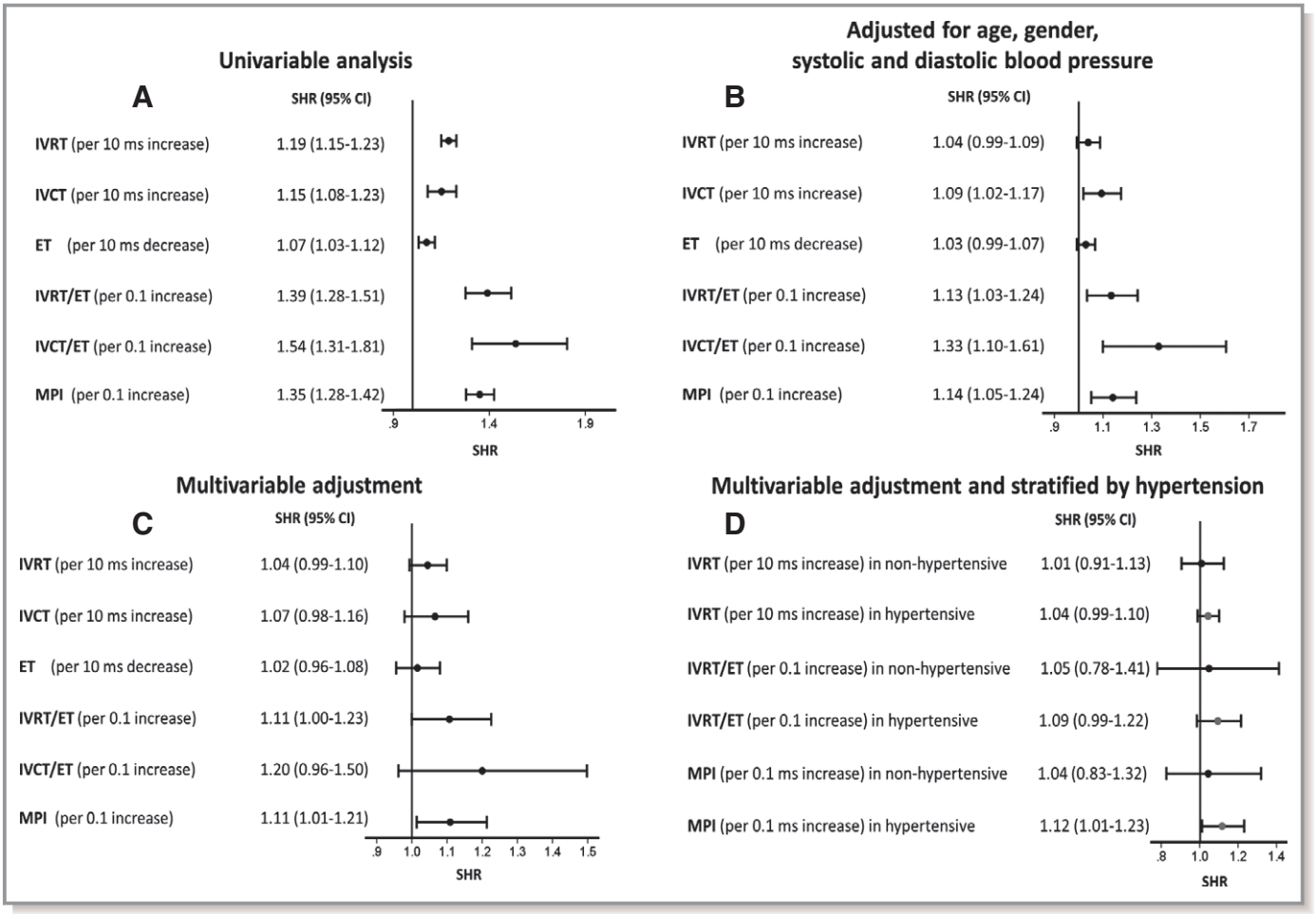

Figure 8. The cardiac time intervals as predictors of future ischemic cardiovascular disease (ICVD). Depicting the subdistribution hazard ratios (SHRs) obtained from univariable analysis (A), adjusted for age, sex, systolic and diastolic blood pressures (B), and multivariable (C) competing risk Cox proportional hazards regression models describing the cardiac time intervals as predictors of future hypertension-related ICVDs. The IVRT, IVRT/ET, and MPI are also stratified according to hypertension status (D). Multivariable adjustment indicates adjustment for age, sex, body mass index, estimated glomerular filtration rate, heart rate, hypertension, systolic blood pressure, diastolic blood pressure, diabetes, cholesterol, smoking status, atrial fibrillation, ischemic heart disease, previous ischemic stroke, left ventricular ejection frasction <50%, diastolic dysfunction, and left ventricular hypertrophy. Depicts the SHRs and the 95% CIs. ET indicates ejection time; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; MPI, myocardial performance index.

and MPI to be the only cardiac time intervals demonstrating impaired cardiac function in patients with hypertension, despite a normal systolic function.[37] Unfortunately, Caccia-puoti and colleagues did not evaluate the diagnostic utility of IVRT/ET in their study[37]; if they had, it would most likely also be impaired in the hypertensive group.

We found a significant linear dose–response relationship, between increasing severity of elevated BP and incremental impairment in cardiac function determined by the age- and sex-adjusted cardiac time intervals (IVRT, IVRT/ET, and MPI) (Figure 4). Even after multivariable adjustment for all other clinical and conventional echocardiographic parameters, this pattern of incremental increase in cardiac dysfunction deter-mined by IVRT, IVRT/ET, and MPI, with increasing severity of elevated BP, remained statistically significant.

Likewise, a previous study demonstrated that MPI increased with increasing severity of hypertension according to LV geometry.[38] Accordingly, we found that all the cardiac time intervals displayed impaired cardiac function with increasing values of the LVMI (Figure 5) even after multivari-able adjustment. In addition, the IVRT/ET and the MPI displayed cardiac dysfunction after multivariable adjustment in all pathological LV geometry groups (Figure 6). These findings of incremental impairment of the cardiac time intervals (especially the IVRT/ET and MPI) with increasing BP and LVMI (Figure 5), and in all types of pathological LV geometry, are important, because a potential future echocar-diographic parameter for risk stratification in hypertension should display incremental impairment in the measure with increasing BP and LVMI and in all types of pathological LV

geometry, as the risk of ICVD increases continuously with increasing BP[5] and LVH.[7,8]

In addition, another central observation in our study was that IVRT and MPI were capable in detecting miniscule cardiac dysfunction in participants with high-normal BP compared with participants with normal BP, when confining our analysis to participants without hypertension and after adjustment for clinical variables. This is important because it has previously been demonstrated that persons with high-normal BP have an increased risk of developing future hypertension[39] and an increased risk of ICVD.[40] Thus, IVRT and MPI reveal impaired cardiac function in persons with high-normal BP. Therefore these time intervals may aid in the early identification of persons in high risk of future fulminant hypertension and ICVDs.

Cardiac Time Intervals and the Risk for ICVD

It is well known that hypertension is associated with increased risk of ICVD[3]; however, the usefulness of the cardiac time intervals to predict future ICVDs in the general population and in participants with hypertension is unknown. We found that only the combined indexes containing information on both systolic and diastolic performance (IVRT/ET and MPI) were independent predictors of future ICVDs, even after adjustment for hypertension status, LVH, SBP, and DBP (Table S1 and Figure 8C). Consequently, even though the IVRT/ET and MPI both are independently associated with BP severity and LVMI, they provide independent and incremental prognostic information to both BP and LVH. The superiority of the IVRT/ET and the MPI to predict future ICVDs may be because they detect miniscule impairment in the myocardial function, regardless of whether the myocardium has an ailing systolic or diastolic function.[19] In the ailing myocardium, the cardiac time intervals will change during disease progression.[41–44] As LV systolic function deteriorates, the IVCT will be prolonged, because it takes longer for the myocardial myocytes to achieve an LV pressure equal to that of the aorta.[44] Further, the ability of myocardial myocytes to maintain a high LV pressure decreases, resulting in reduction in the ET.[44] As LV diastolic function becomes impaired, early diastolic relaxation proceeds more slowly, explaining the prolongation of the IVRT. Consequently, the IVRT/ET and the MPI, defined as [(IVCT+IVRT)/ET], will detect cardiac dysfunction with an increase, regardless of whether the LV has impaired systolic or diastolic function.[45,46] Therefore, in the general population, the IVRT/ET and MPI identifies subtle impairments in the cardiac function (both systolic and diastolic) that may be unnoticed with conventional echocardiography[13,14](Figure 3) and can improve risk stratification strategies evaluating future risk of fulminant hypertension-related ICVDs incremental to the traditional predictors. In accordance with this, adding IVRT/ET or MPI to the clinical predictors from the Framingham Risk Score,[32] the SCORE risk chart,[34] and the ESH/ESC risk chart[1] yielded better predicting models with significant increases in the categorical net reclassification improvements. However, we found that hypertension significantly modified the relationship between all the cardiac time intervals containing information about diastolic function (IVRT, IVRT/ET, and MPI) and the risk of future ICVDs. These cardiac time intervals primarily predicted hypertension-related ICVDs in participants with hypertension but not in participants without hypertension (Figure 8D). Similarly, a previous study demonstrated that the presence of diastolic dysfunction, determined by a short deceleration time, predicted all-cause mortality only in hypertensive heart failure patients and not in heart failure patients without hypertension.[47] Therefore, in participants with hypertension, who are in particularly high risk of future ICVDs,[3] the IVRT/ET and MPI may be useful cardiac measures for risk stratification. They are simple to obtain, have high reproducibility,[19,21,22] and encompass information on BP severity, LV geometry, and risk of future ICVDs.

Limitations

The inhabitants of Denmark and the study population are primarily white, which limits the generalizability of our findings to other general populations with other race/ethnicity compositions.

Participants with short-lived or prolonged periods of hypertension were treated similarly in the analyses. It would be relevant to know who were well controlled during the follow-up period because this might have influenced the incidence of ICVDs. Unfortunately, this information was not collected. We, however, adjust for the SBP and DBP at baseline in our multivariable models, and uncontrolled hypertension at baseline is therefore taken into account in the present report.

Conclusion

The cardiac time intervals (especially the IVRT, IVRT/ET, and MPI) displayed a significant dose–response relationship, with increasing severity of elevated BP and increasing LVMI. Further, they identified impaired cardiac function in participants with hypertension, not only independent of conventional risk factors but also in participants with a normal conventional echocardiographic examination. Additionally, in the general population, the IVRT/ET and MPI are powerful and independent predictors of future hypertension-related ICVDs, especially in participants with known hypertension. They provide prognostic information incremental to clinical variables from the Framingham Risk Score, the SCORE risk chart, and the ESH/ESC risk chart.

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Disclosures

None.

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