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Archeological Echocardiography: Digitization and Speckle-Tracking Analysis of Archival Echocardiograms in the HyperGEN Study

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Abstract

Background—Several large epidemiologic studies and clinical trials have included echocardiography, but images were stored in analog format and these studies predated tissue Doppler imaging (TDI) and speckle-tracking echocardiography (STE). We hypothesized that digitization of analog echocardiograms, with subsequent quantification of cardiac mechanics using STE, is feasible, reproducible, accurate, and produces clinically valid results.

Methods—In the NHLBI HyperGEN study (N=2234), archived analog echocardiograms were digitized and subsequently analyzed using STE to obtain tissue velocities/strain. Echocardiograms were assigned quality scores and inter/intraobserver agreement was calculated. Accuracy was evaluated in (1) a separate second study (N=50) comparing prospective digital strain vs. post-hoc analog-to-digital strain; and (2) in a third study (N=95) comparing prospectively-obtained TDI e' velocities with post-hoc STE e' velocities. Finally, we replicated previously known associations between tissue velocities/strain, conventional echocardiographic measurements, and clinical data.

Results—Of the 2234 HyperGEN echocardiograms, 2150 (96.2%) underwent successful digitization and STE analysis. Inter/intraobserver agreement was high for all STE parameters, especially longitudinal strain (LS). In accuracy studies, LS performed best when comparing post-hoc STE to prospective digital STE for strain analysis. STE-derived e' velocities correlated with, but systematically underestimated, TDI e' velocity. Several known associations between clinical variables and cardiac mechanics were replicated in HyperGEN. We also found a novel independent inverse association between fasting glucose and LS (adjusted $\beta = -2.4$ [95% CI $-3.6, -1.2$] % per 1-SD increase in fasting glucose; $P < 0.001$).

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DISCLOSURES

None.

Conclusions—Archeological echocardiography, the digitization and speckle-tracking analysis of archival echocardiograms, is feasible and generates parameters of cardiac mechanics similar to contemporary studies.

Keywords

ventricular mechanics; strain; speckle-tracking echocardiography; epidemiology

INTRODUCTION

Speckle-tracking echocardiography (STE) is a novel technique for the assessment of cardiac mechanics and has been validated by several methods, including sonomicrometry and tagged cardiac magnetic resonance imaging.[1, 2] By quantifying indices of cardiac mechanics, such as peak longitudinal, circumferential, and radial systolic strain, and diastolic and systolic tissue velocities, STE can be used to phenotype and detect subclinical cardiac dysfunction at an early stage, prior to the development of overt cardiac dysfunction or symptomatic heart failure. Furthermore, abnormalities in strain parameters can provide insight into the relationship between risk factors (such as hypertension) and ventricular dysfunction, and reduced strain has been shown to predict adverse events.[3, 4] A distinct advantage of STE over other imaging modalities is the ability to post-process archival echocardiograms that were performed in the past as part of large-scale population-based studies and clinical trials. Thus, novel studies of cardiac mechanics may be possible with the application of STE to archival echocardiograms, a process that can be considered to be a form of “archeological” echocardiography.

The Hypertension Genetic Epidemiology Network (HyperGEN) study, conducted from 1996–2002, provides a robust platform for the study of cardiac mechanics in systemic hypertension through the use of STE analysis. Originally designed to determine the genetic basis of hypertension and left ventricular (LV) hypertrophy, the HyperGEN study holds several advantages for studying cardiac mechanics, including a large sample of African Americans and whites, comprehensive clinical and laboratory data collection, and 2-dimensional (2D) and Doppler echocardiographic data.[5] HyperGEN echocardiograms were performed and stored on videotape at a time prior to digital storage, tissue Doppler imaging (TDI), and STE. Conversion of HyperGEN echocardiograms from analog to digital format would allow and the application of STE analysis to these echocardiograms.

Therefore, we sought to determine whether digitization and subsequent quantification of cardiac mechanics using archived echocardiograms from a large population-based epidemiologic study like HyperGEN study is possible. We hypothesized that digitization and STE of archival echocardiograms: (1) is feasible; (2) is reproducible, with reasonable inter- and intraobserver variability; (3) compares favorably to prospective digital STE and TDI; and (4) is able to validate previously documented associations between cardiac mechanics, acquired risk factors, and conventional echocardiographic parameters.

METHODS

Study Population

HyperGEN, part of the National Institutes of Health Family Blood Pressure Program (FBPP), is a cross sectional-study consisting of four U.S. sites (Salt Lake City, Utah; Forsyth County, NC; Minneapolis, Minnesota; and Birmingham, Alabama). The goal of HyperGEN was to identify and characterize the genetic basis of familial hypertension; complete details of the HyperGEN study design have been reported previously.[5] Study eligibility required a diagnosis of hypertension prior to the age of 60 and at least one sibling willing to participate in the study. Hypertension was defined as an average systolic blood pressure ≥ 140 mmHg or an average diastolic blood pressure ≥ 90 mmHg (on at least 2 separate clinic visits) or by self-reporting treatment for hypertension. Age-matched normotensive participants were also enrolled as control subjects. Individuals with a history of type 1 diabetes mellitus or severe chronic kidney disease were excluded. Echocardiography was performed as part of an ancillary study to HyperGEN. For the present study, we analyzed the echocardiograms of 2234 HyperGEN participants. All HyperGEN study participants gave written informed consent, and the HyperGEN study was approved by each study site's local institutional review board.

Clinical and Echocardiographic Characteristics

Demographic, clinical, laboratory, and echocardiographic characteristics as well as medication history were all collected during the initial HyperGEN visit. Diabetes mellitus was defined by fasting glucose ≥ 126 mg/dl, use of hypoglycemic medication, or a self-reported history. History of myocardial infarction and stroke were self-reported. Doppler, 2D, and M-mode echocardiograms were acquired using standardized acquisition protocols and stored in analog format (high grade, medical quality videocassette tapes) at the time of visit.[6, 7] Cardiac structure and function were quantified as recommended by the American Society of Echocardiography (ASE).[8–10] LV mass was calculated using the ASE-recommended formula for LV linear dimensions and indexed to body surface area. LV hypertrophy was defined as LV mass index ≥ 96 g/m² in women and ≥ 116 g/m² in men.[9] Relative wall thickness was calculated as $2 \times \text{posterior wall thickness} / \text{LV end-diastolic dimension}$. Circumferential LV midwall end-systolic stress was calculated using the method of Shimuzu et al.[11] Conventional diastolic function parameters included transmitral flow characteristics and isovolumic relaxation time. Wall motion was also scored on all echocardiograms.

Digitization and Interpretation of Image Quality

Archived echocardiograms in analog format were converted to digital format (digitized) using the TIMS 2000 DICOM System (Foresight Imaging, Chelmsford, MA). Cine loops of 2–4 cardiac cycles from the parasternal short axis (papillary muscle level) in addition to apical two, three, and four chamber views were digitized at a frame rate of 30–40 frames per second (fps) and stored offline in DICOM format. Each study was assessed for image quality by an experienced operator, blinded to all other clinical and echocardiographic data, using a 4-point scale based on the degree of endocardial border visualized (1 = 0–25%; 2 = 25%–50%; 3 = 50%–75%; 4 = 75%–100%), similar to scales used previously.[12, 13]

Two-Dimensional Speckle-Tracking Analysis

Digitized cine loops were analyzed using 2D wall motion tracking software [2D Cardiac Performance Analysis (CPA), TomTec v4.5, Unterschleissheim, Germany]. After isolating the highest quality cardiac cycle, the endocardial and epicardial borders were traced at end-systole in each view. Computerized speckle-tracking analysis was performed, and endocardial and epicardial border tracings were adjusted to optimize tracking. Tracking quality was scored using a four-point scale based on the adequacy of tracking by visual estimation (1 = poor tracking; 2 = fair tracking; 3 = moderate tracking; 4 = excellent tracking).[14] Longitudinal, global radial, and global circumferential strains, and early diastolic tissue velocities (septal and lateral e'), were recorded. The complete digitization and speckle-tracking workflow is depicted in Figure 1. For ease of reporting, all strain values are presented as absolute values (i.e., the lower the absolute strain value, the worse the strain value).

Comparison of Longitudinal Strain Measured in the Apical 4-, 3-, and 2-Chamber Views

In order to determine whether longitudinal strain measured in the apical 4-chamber view correlates sufficiently well to longitudinal strain measured in the apical 3- and 2-chamber views, STE analysis was performed on all 3 views in 50 HyperGEN participants who were free of wall motion abnormalities.

Validation of Cardiac Mechanics Derived from Archival Echocardiograms

Figure 1 displays the workflow of 2 validation studies to determine how 2D CPA on archived echocardiograms performed in comparison to prospective digital STE and TDI (Study #2 and Study #3 in Figure 1, respectively). To validate the use of the 2D CPA software for the determination of strain parameters using STE, we compared it with EchoPAC software (GE Medical Systems, Milwaukee, WI) which has been well-validated and most commonly used in the literature.[1, 4, 15–18] EchoPAC cannot be used in HyperGEN because it requires prospective echocardiographic imaging with a GE echocardiography machine prior to STE analysis.

We performed our strain validation in 50 consecutive patients who underwent clinically indicated echocardiography at the Bluhm Cardiovascular Institute at Northwestern Memorial Hospital (Chicago, Illinois). All patients were first imaged using a Vivid 7 echocardiography system with an M3S probe (GE Medical Systems, Milwaukee, WI) at frame rate of 30–40 fps to mimic the frame rate of the HyperGEN echocardiograms. All images were stored digitally and on S-VHS videotapes. We then compared STE of digitized-VHS echocardiograms (analogous to HyperGEN echocardiograms) versus native digital speckle tracking on EchoPAC. All analyses were done in a blinded fashion to minimize bias.

We also performed a comparison of STE-derived basal longitudinal tissue velocities versus tissue Doppler velocities of the mitral annulus. Prospective digital echocardiography, including TDI, was performed on 95 consecutive patients who presented for exercise stress testing at the Northwestern Bluhm Cardiovascular Institute. Echocardiograms were performed using a SONOS 7500 ultrasound machine with an S8 probe (Philips Healthcare, Andover, MA). Only the baseline, resting echocardiograms were analyzed. None of the

study patients had significant valvular disease. The prospective digital pulse-wave tissue Doppler e' velocities at the septal and lateral mitral annulus were recorded on each study patient. All 95 echocardiograms were subsequently analyzed with 2D CPA software, blinded to the TDI results.

All patients recruited into the STE and TDI validation studies gave written informed consent, and these studies were approved by the Northwestern University institutional review board.

Statistical Analysis

Clinical characteristics, laboratory data, and both conventional echocardiographic parameters and STE-derived parameters were summarized for the entire HyperGEN study sample. Continuous data were presented as mean $\pm$ standard deviation. Categorical variables were presented as a count and percentage.

We evaluated inter- and intraobserver reliability in a randomly selected sample of 96 HyperGEN participants. These echocardiograms were analyzed by 2 independent readers, blinded to each other's measurements, and all other data. For the purposes of intraobserver reliability, all 96 echocardiograms were re-analyzed (in random order) by 1 of the readers, 1 month after initial STE analysis. Reliability of STE measurements was evaluated using the intraclass correlation coefficient (ICC), mean bias, and coefficient of variation.

Pearson correlation coefficients were calculated, and Bland-Altman analyses were performed, to compare (1) longitudinal strain derived from the apical 4-chamber view versus the apical 3- and 2-chamber views; (2) strain measurements made using prospective digital EchoPAC STE versus VHS-to-digital conversion with subsequent analysis with 2D CPA software; and (3) e' velocity measurements made using prospective TDI versus post-hoc STE.

To clinically validate the utility of STE-derived measurements, previously known associations between clinical and conventional echocardiographic variables and tissue velocities/strain were replicated in HyperGEN using linear mixed-effects models to account for relatedness among HyperGEN study participants. All HyperGEN analyses were adjusted for reader, image quality, and study site (to account for differences in echocardiography machines and sonographers). A statistical test with p -value < 0.05 was considered statistically significant. Analyses were performed using Stata version 12.0 (StataCorp, College Station, TX) and SAS statistical software version 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

Feasibility, Image Quality, and Tracking Quality

Of the 2234 HyperGEN echocardiograms analyzed, 2150 (96.2%) underwent successful digitization and STE analysis (84 echocardiograms were on analog tapes that were damaged and therefore unreadable). Image quality was high (image quality score > 2) in 62.8% of parasternal short-axis views and 80.4% of apical 4-chamber views. Only 3% of apical 4-chamber views were of low quality (image quality score = 1). Likewise, tissue tracking

quality was considered at least adequate (≥ 2) in 93.8% of parasternal short-axis views and 96.6% of apical 4-chamber views.

Clinical and Echocardiographic Characteristics of the HyperGEN Study Participants

Table 1 displays the clinical characteristics of the HyperGEN study participants who underwent successful digitization and STE analysis (N=2150). The mean age was 51 ± 14 years, 58% were female, and 46% were African American. Hypertension was common, but blood pressure was well controlled in the majority of study participants. Hyperlipidemia and obesity were also common. Laboratory results revealed largely preserved kidney function (estimated glomerular filtration rate [eGFR] 85 ± 20 ml/min/1.73 m²) and mildly elevated fasting glucose (114 ± 55 mg/dl).

Echocardiographic parameters (Table 2) demonstrated normal LV volumes and ejection fraction in most study participants, with LV hypertrophy present in 20% of the participants, reflecting the high prevalence of hypertension in HyperGEN. Diastolic function parameters fell in the range of normal or pseudonormal with E/A ratio > 1 in the majority of study participants. Early diastolic (e') tissue velocities, however, which were derived from STE, were consistent with abnormal diastolic function in a large number of participants.

Reproducibility

Table 3 displays the results of inter- and intraobserver reliability analyses for strain parameters and e' tissue velocities, performed on a random subset of 96 unrelated HyperGEN participants. Mean bias for inter- and intraobserver comparisons was low for all parameters, with no evidence of systematic bias on Bland-Altman analysis (Supplemental Figures S1 and S2). ICC values were high (> 0.75) for intraobserver comparisons on all STE parameters, but highest for longitudinal and global radial strains. On interobserver variability analysis, ICC was highest for global radial strain, though ICC values were high (> 0.75) for all other STE parameters as well. Inter- and intraobserver coefficient of variation values were lowest for longitudinal strain and highest for lateral e' velocity. These data show that reproducibility was high for all STE parameters, and that longitudinal strain had the lowest inter- and intraobserver variability.

Apical 4- vs. Apical 3- and 2-Chamber Views for Longitudinal Strain

The apical 4-, 3-, and 2-chamber views from the echocardiograms of 50 unrelated HyperGEN participants were analyzed using STE to determine whether LS measurements derived from the apical four chamber view were consistent with those from the apical 3- and 2-chamber views. As shown in Table 4, correlation was high, and mean bias low, for the comparisons between LS measured in the apical 4-chamber vs. the apical 3- and 2-chamber views (and vs. global LS, derived from all 3 views). Supplemental Figure S3 displays the scatterplots and Bland-Altman plots for the comparison of LS in the apical views.

Validation of Analog-to-Digital Conversion with Subsequent Speckle-Tracking Analysis

To validate the use of the VHS-to-digital conversion with subsequent 2D CPA software analysis for measurement of strain, we compared it with prospective digital EchoPAC software analysis in 50 consecutive patients referred for clinically indicated

echocardiography. As shown in Table 4 and Figure 2, there was high correlation, and minimal bias, between 2D CPA and EchoPAC for longitudinal strain. Correlation was also high, and bias was low, for global radial strain. However, the correlation coefficient for global circumferential strain was modest ($R=0.58$) and there was a systematic bias with over-estimation of strain values by 2D CPA (mean bias +5.3%) compared to EchoPAC (Figure 2).

To validate the use of the 2D CPA software analysis for measurement of e' velocity, we compared it with prospective digital TDI in 95 consecutive patients referred for clinically indicated echocardiography. As shown in Table 4 and Figure 3, measurements made with STE showed good correlation with those from TDI for both septal and lateral e' velocities. However, 2D CPA STE systematically underestimated TDI in our study, a finding that was more exaggerated on lateral e' velocity measurements. There was also a systematic bias towards larger underestimation by STE at higher lateral e' velocity values (Figure 3). Using linear regression analysis, we derived the following equations to convert STE-derived e' velocities to values that are comparable to values obtained by TDI: septal e' (corrected) = 1.4 (septal STE e') + 1.9 ; lateral e' (corrected) = 1.6 (lateral STE e') + 5.0 .

Replication of Previously Reported Associations

Table 5 shows the results of a replication analysis of associations between clinical variables and STE parameters (longitudinal strain and e' velocity) that were previously reported in a population-based study by Dalen et al.[19] In general, previously reported associations were replicated in HyperGEN. Specifically, increases in age (in men only), body-mass index, systolic blood pressure, diastolic blood pressure, non-HDL cholesterol, and HDL cholesterol (in women only) were all found to be associated with reductions in longitudinal strain. The inverse association between eGFR and longitudinal strain reported in the study by Dalen et al. was not replicated in HyperGEN.

On analysis of associations with e' velocity, findings in HyperGEN were similar to the study by Dalen et al. for age, systolic blood pressure, diastolic blood pressure, non-HDL cholesterol (in women only), and HDL cholesterol (in women only). Associations were absent or attenuated for body-mass index and eGFR (though there was a statistically significant association between eGFR and e' velocity in women in HyperGEN, which was not present in the study by Dalen et al.).

In the prior study by Dalen et al., glucose was found to be associated with e' velocity in men but not women, and glucose was not associated with longitudinal strain.[19] In HyperGEN, we found a novel inverse association between fasting glucose and longitudinal strain in both men and women (Table 5). There was a similar inverse association between fasting glucose and e' velocity in HyperGEN as well. In the entire HyperGEN cohort (men and women combined), fasting glucose was inversely associated with longitudinal strain even after adjusting for age, sex, body-mass index, and history of diabetes ($\beta=-2.4$ [95% CI -3.6 , -1.2]% per 1-standard deviation increase in fasting glucose; $P<0.001$). The association between fasting glucose and longitudinal strain was also present in the subset of non-diabetic HyperGEN participants ($P<0.001$).

Finally, in comparison to a study of STE in mild hypertension,[20] our analysis of HyperGEN replicated all previously reported associations between conventional echocardiographic parameters and global circumferential and longitudinal strains (Table 6).

DISCUSSION

In a comprehensive study of 2150 participants from the HyperGEN study and 2 subsequent validation studies involving a total of 145 patients, we demonstrate the feasibility, reliability, and validity of archeological echocardiography—the use of STE to post-process archival echocardiograms for the determination of tissue velocities and strain. To our knowledge, our study is the first to show that digitization and STE of echocardiograms archived on analog videotapes is feasible and provides reproducible and valid results. In addition, in our proof-of-concept feasibility study, we found a novel inverse association between fasting glucose and longitudinal strain in HyperGEN, the first time such an association has been reported in a population-based study. The association between fasting glucose and reduced longitudinal strain demonstrates the utility of speckle-tracking analysis on archival echocardiograms. In an era of limited funding resources for scientific investigation, the use of STE on archival echocardiograms from previously completed epidemiologic studies and clinical trials, as we have done in HyperGEN, could be a cost-effective way to broaden understanding of cardiac mechanics in normal individuals and in a large variety of disease states.

Feasibility and Reproducibility

Measurement of strain and tissue velocities was feasible in the vast majority (>95%) of HyperGEN participants with good endocardial resolution as assessed by image quality score. Inter- and intraobserver agreement was high across all STE parameters, especially for longitudinal strain, which had the lowest coefficient of variation as well, similar to a previous large speckle-tracking study.[21] In addition, we found that STE of the apical 4-chamber alone to measure longitudinal strain is reasonable in the presence of normal wall motion given the high correlation and minimal bias in our comparison of longitudinal strain measured in the apical 4- vs. the apical 3- and 2-chamber views.

Validity of Post-Processing Speckle-Tracking Echocardiography when Compared to Prospective Digital Tissue Doppler Imaging and Speckle-Tracking Echocardiography

In our 2 validation studies of strains and tissue velocities (N=50 and N=95, respectively), we found that analog-to-digital conversion, with subsequent STE, performed relatively well when compared to prospective digital STE and TDI. 2D CPA resulted in similar longitudinal strain measurements when compared to EchoPAC. similar to the results of a previous study. [22] Correlation coefficients were high for all parameters except for global circumferential strain. Mean bias was low for longitudinal and radial strain. However, post-hoc STE overestimated global circumferential strain with a mean bias of +5.3%. There are a few potential reasons for the lower inter-software correlations for global circumferential strain, as discussed in a previous study that found a similar result.[22] First, out-of-plane motion of echocardiographic acoustic markers in the short axis likely limits consistency between algorithms in software packages, which may affect circumferential strain more than radial strain. In addition, the array of myofiber orientation in the left ventricular myocardium is

heterogeneous and therefore differences in the exact tracking segments between software may become important.

Post-hoc STE compared well to TDI for the measurement of e' velocity, confirming the results of a previous study using another software package.[23] However, there was a systematic underestimation of e' velocity. The underestimation by STE compared to pulse-wave TDI is likely because STE (similar to color Doppler TDI) measures the average velocity within a segment of the myocardium, whereas pulse-wave TDI measures the peak velocity within a segment of the myocardium. Another reason for the underestimation of e' velocities by STE could be the lower frame rate of STE compared to TDI; however, one would expect that there would be an underestimation of all post-hoc STE parameters if this was the case, and we found that post-hoc STE analysis of strain parameters were similar (or overestimated) prospective digital STE.

Clinical Validation

Although demonstrating feasibility, reproducibility, and accuracy of the archeological echocardiography methodology is important, replication of previously known associations between clinical variables and tissue velocities/strain is perhaps most important in showing the clinical validity and utility of our methods. We therefore compared HyperGEN to a high-quality, large, population-based study (Nord-Trøndelag Health Study [HUNT]), which included prospective digital STE and TDI on 1296 individuals free of cardiovascular disease, diabetes, or hypertension.[19] We were able to replicate associations between several clinical variables (including age, body-mass index, blood pressure, and non-HDL cholesterol) and longitudinal strain and e' velocity in HyperGEN. Differences in the strength of association between studies likely could be explained by the retrospective vs. prospective nature of HyperGEN and HUNT, respectively, and differences in study populations. For example, 46% of HyperGEN participants were of African descent and HUNT participants were all of European descent, eGFR was higher in HyperGEN, and laboratory testing was done in the fasting state in HyperGEN but not in HUNT. Nevertheless, the consistency of the results between the 2 studies provides external validity of the methods used in HyperGEN for the measurement of indices cardiac mechanics.

In comparison to 2 high-quality studies which evaluated the correlation between conventional echocardiographic parameters and strain parameters,[4, 20] findings from HyperGEN compared favorably. For global circumferential strain, associations with LV mass and circumferential end-systolic stress were replicated, with slightly attenuated correlation coefficients. The association between relative wall thickness and global circumferential strain was significant in HyperGEN but not in the prior study by Narayan et al.,[20] likely due to the larger sample size of HyperGEN. For longitudinal strain, all correlations with conventional echocardiographic parameters (LV mass, wall motion score index, and LV ejection fraction) were replicated, but the strength of the correlations was attenuated in HyperGEN, as expected given the comparison of post-hoc (HyperGEN) to prospective digital STE in the 2 prior studies by Narayan et al. and Stanton et al.[4, 20] It is important to note that the values of most longitudinal and radial strain parameters were

lower than values obtained using prospective STE in Narayan's study of patients with mild hypertension.[20]

Finally, in HyperGEN, we found a novel independent inverse association between fasting glucose and longitudinal strain, an association that was present even in non-diabetics. Prior studies have reported reductions in longitudinal strain and tissue velocities in diabetics,[24–26] but to our knowledge, the relationship between fasting glucose and longitudinal strain has not been reported in a population-based study or in non-diabetics. A recent study in diabetic patients revealed delayed longitudinal contractile function (indicated by worse longitudinal strain) after dobutamine stress testing compared to non-diabetic patients, supporting the hypothesis of the pathogenic milieu induced by the hyperglycemic environment.[27] Our results indicate that the study of hyperglycemia on cardiac mechanics may provide insight into the effects of insulin resistance on myocardial function prior to the onset of diabetes. Given the burgeoning rates of obesity and insulin resistance worldwide, the study of hyperglycemia and its effects on longitudinal strain may benefit from further evaluation in epidemiologic and observational clinical studies, and in clinical trials of anti-diabetic drugs.

Limitations

Although the present study demonstrates the accuracy of secondary analysis using the 2D CPA software, several limitations must be considered. Despite the fidelity of the analog-to-digital conversion technique, we were only able to acquire images at a frame rate of 30–40 fps. Because obtaining accurate strain and e' tissue velocity data is dependent on the position of speckles from frame to frame, large differences in speckle patterns between sequential frames can introduce variability. Furthermore, STE depends on good image quality. However, unlike digital images, echocardiograms stored in analog format are susceptible to deterioration over time, resulting in poorer image quality once converted from analog to digital format. Nonetheless, we were able to show that despite these challenges, images of adequate quality can be collected in a large number of study participants; the measured parameters correlate well with prospective digital measurement of strains and tissue velocities; and we were able to replicate several previously known associations between clinical and conventional echocardiographic variables with strain parameters and e' velocities. Finally, it should be noted that given the variability of image quality, tracking quality, and performance of post-hoc STE, the process of archeological echocardiography will likely work best in studies like HyperGEN that have large sample sizes which can help mitigate the noise in the post-hoc STE data.

Conclusions

Secondary analysis of archival echocardiograms using analog-to-digital conversion and post-hoc STE for the measurement of cardiac mechanics is feasible, reproducible, accurate, and able to replicate previously known associations between clinical variables and STE-derived parameters. Given the large number of high-quality epidemiology studies and clinical trials that have included echocardiography over the past 30 years, “archeological echocardiography” holds great promise as a technique capable of producing novel insights into the genetics, risk factors, and natural history of abnormal cardiac mechanics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Workflow Diagram for HyperGEN Digitization/Speckle-Tracking Analysis (Study #1) and Validation Studies (Study #2 and Study #3)

HyperGEN = Hypertension Genetic Epidemiology Network; 2D CPA = TomTec 2D Cardiac Performance Analysis software; STE = speckle-tracking echocardiography; LS = longitudinal strain; GCS = global circumferential strain; GRS = global radial strain; A4c = apical 4-chamber view; A3c = apical 3-chamber view; A2c = apical 2-chamber view; EchoPAC = General Electric (GE) EchoPAC software; TDI = tissue Doppler imaging

Figure 2.

Comparison of Digital Speckle-Tracking Echocardiography (EchoPAC Software) versus Analog-to-Digital Conversion with Subsequent Speckle-Tracking Echocardiography (2D Cardiac Performance Analysis Software): Scatterplots and Bland-Altman Plots

Post-hoc speckle-tracking analysis correlated best with prospective digital EchoPAC for longitudinal strain and global radial strain. The correlation was weaker for global circumferential strain, and there was an over-estimation bias as shown in the Bland-Altman plot. LS = longitudinal strain; GCS = global circumferential strain; GRS = global radial strain

Figure 3.

Comparison of Tissue Doppler Imaging versus Analog-to-Digital Conversion with Subsequent Speckle-Tracking Echocardiography (2D Cardiac Performance Analysis Software): Scatterplots and Bland-Altman Plots

Post-hoc speckle-tracking analysis correlated better with septal e' velocity compared to lateral e' velocity. Speckle-tracking echocardiography underestimated tissue Doppler imaging for the measurement of e' velocity (lateral > septal), with a larger underestimation at higher lateral e' velocities, as shown in the Bland-Altman plot. Equations for converting speckle-tracking echocardiography e' velocity values to tissue Doppler e' velocity values are shown next to the scatterplots for both septal and lateral e' velocities. TDI = tissue Doppler imaging; STE = speckle-tracking echocardiography.

Table 1

Clinical Characteristics of the Study Sample

Characteristic	All participants (N=2150)
Age, y	51±14
Female, n (%)	1255 (58)
Race/ethnicity, n (%)	
• White	1144 (53)
• African-American	999 (46)
• Other	7 (<1)
Study center, n (%)	
• Birmingham, Alabama	590 (27)
• Salt Lake City, Utah	589 (27)
• Winston-Salem, North Carolina	545 (25)
• Minneapolis, Minnesota	426 (20)
Comorbidities, n (%)	
• Hypertension	1251 (58)
• Dyslipidemia	1310 (61)
• Obesity (body-mass index > 30 kg/m ²)	1021 (47)
• Diabetes mellitus	365 (17)
• Stroke	97 (5)
• Chronic kidney disease (GFR < 60 ml/min/1.73 m ²)	197 (9)
• Myocardial infarction	131 (6)
Physical examination:	
• Systolic blood pressure, mm Hg	127±21
• Diastolic blood pressure, mm Hg	72±11
• Body-mass index, kg/m ²	31±7
Laboratory data:	
• Sodium, mEq/L	142±2
• Estimated GFR, ml/min per 1.73m ²	85±20
• Fasting glucose, mg/dl	106±43
• Total serum cholesterol, mg/dl	196±39
• High-density lipoprotein cholesterol, mg/dl	50.6±15.1
• Low-density lipoprotein cholesterol, mg/dl	118.7±34.4
• Triglycerides, mg/dl	140.0±97.8

GFR = glomerular filtration rate

Table 2**2D/Doppler and Speckle-Tracking Echocardiographic Parameters in HyperGEN**

Echocardiographic parameter	All participants (N=2150)
2D/Doppler parameters:	
• LV end-systolic volume, ml	51±23
• LV end-diastolic volume, ml	130±31
• LV ejection fraction, %	62±8
• LV mass index, g/m ²	41±12
• LV hypertrophy, n (%)	438 (20)
• Left atrial diameter, cm	3.5±0.55
• E velocity, cm/s	72.8±19.6
• A velocity, cm/s	66.1±18.8
• E/A ratio	1.2±0.5
• E deceleration time, ms	204±58
• Isovolumic relaxation time, ms	80±18
• Wall motion abnormality, n (%)	145 (7)
Speckle-tracking parameters:	
• Global radial strain, %	26.6±11.9
• Global circumferential strain, %	20.6±5.3
• Longitudinal strain, %	14.6±3.6
• Septal e' velocity, cm/s	7.1±1.9
• Lateral e' velocity, cm/s	10.5±2.0
• Septal E/e' ratio	10.6±3.5
• Lateral E/e' ratio	7.0±1.9

LV = left ventricular; E = early diastolic; A = late (atrial) diastolic

All strain measurements are presented as absolute values for ease of presentation and interpretation. Septal and lateral e' velocities were converted from raw values that correspond to tissue Doppler velocities using conversion equations (see text for details).

Table 3

Reproducibility of Speckle-Tracking Echocardiography Parameters (N=96)

Parameter	Interobserver Reliability				Intraobserver Reliability			
	Mean±SD	ICC (95% CI)	Mean bias (95% CI)	CV	ICC (95% CI)	Mean bias (95% CI)	CV	
LS, %	15.3±2.7	0.77 (0.69, 0.85)	0.71 (0.34, 1.08)	9.9%	0.90 (0.87, 0.94)	-0.17 (-0.46, 0.11)	7.2%	
GCS, %	21.6±5.0	0.76 (0.67, 0.85)	1.22 (0.52, 1.93)	13.6%	0.88 (0.83, 0.93)	-0.52 (-0.06, 1.09)	9.6%	
GRS, %	27.2±9.7	0.92 (0.89, 0.95)	-0.39 (-1.17, 0.38)	11.1%	0.92 (0.88, 0.95)	0.66 (0.10, 1.42)	11.3%	
Septal e', cm/s	3.4±1.0	0.77 (0.69, 0.86)	0.06 (-0.08, 0.21)	13.8%	0.78 (0.70, 0.85)	0.12 (-0.007, 0.25)	13.7%	
Lateral e', cm/s	2.7±1.1	0.76 (0.67, 0.84)	-0.11 (-0.28, 0.06)	26.9%	0.81 (0.75, 0.88)	-0.09 (-0.24, 0.06)	22.3%	

GCS = global circumferential strain; GRS = global radial strain; LS = longitudinal strain; SD, standard deviation; ICC = intraclass correlation; CI, confidence interval; CV = coefficient of variation

Table 4

Comparison of Strain Parameters Derived from Post-Processed Analog-to-Digital Echocardiograms vs. Prospective Digital Echocardiography and Comparison of Apical 4-Chamber to Apical 3- and 2-Chamber Longitudinal Strain (and Global Longitudinal Strain)

Speckle-tracking parameter	N	Correlation coefficient	P-value	Mean bias (95% confidence interval)
<i>Digital STE (EchoPAC software) vs. analog-to-digital conversion with subsequent STE (2D CPA software)</i>				
• Longitudinal strain	50	0.86	<0.0001	-0.9 (-1.6, -0.3)
• Global circumferential	50	0.58	<0.0001	5.3 (4.1, 6.6)
• Global radial strain i	50	0.72	<0.0001	-0.5 (-3.1, 2.2)
<i>Tissue Doppler imaging vs. analog-to-digital conversion with subsequent STE (2D CPA software)</i>				
• Septal e' velocity	95	0.88	<0.0001	-3.5 (-3.8, -3.2)
• Lateral e' velocity	95	0.72	<0.0001	-7.3 (-8.0, -6.6)
<i>Analog-to-digital STE comparison of A4c to A3c and A2c for longitudinal strain (2D CPA software)</i>				
• A4c vs. A3c	50	0.86	<0.0001	-0.3 (-0.7, 0.05)
• A4c vs. A2c	50	0.86	<0.0001	0.1 (-0.3, 0.5)
• A4c vs. global longitudinal strain	50	0.96	<0.0001	-0.2 (-0.4, 0.1)

* STE = speckle-tracking echocardiography; A4c = apical 4-chamber view; A3c = apical 3-chamber view; A2c = apical 2-chamber view

Table 5
Replication of Known Associations between Clinical Variables and Speckle-Tracking Parameters

Longitudinal strain					Early diastolic (e') velocity*														
Dalen, et al.					HyperGEN					Dalen, et al.					HyperGEN				
Clinical variable	Sex	N	% Change/SD (95% CI) [†]	P	N	% Change/SD (95% CI)	P	N	% Change/SD (95% CI)	P	N	% Change/SD (95% CI)	P	N	% Change/SD (95% CI)	P			
Age	Women	663	-3.9 (-4.9, -2.9)	<0.001	1255	-0.7 (-2.0, 0.5)	0.23	663	-22 (-24, -21)	<0.001	1255	-18 (-20, -16)	<0.001	1255	-18 (-20, -16)	<0.001			
	Men	603	-3.1 (-4.3, -1.9)	<0.001	895	-3.4 (-4.9, -1.8)	<0.001	603	-21 (-22, -19)	<0.001	895	-18 (-20, -16)	<0.001	895	-18 (-20, -16)	<0.001			
Body-mass index	Women	647	-3.1 (-4.1, -2.1)	<0.001	1226	-1.2 (-2.3, -0.1)	0.029	647	-4.4 (-5.8, -2.9)	<0.001	1226	-0.8 (-2.4, 0.8)	0.35	1226	-0.8 (-2.4, 0.8)	0.35			
	Men	594	-3.9 (-5.1, -2.8)	<0.001	886	-2.5 (-4.6, -0.5)	0.018	594	-6.7 (-8.4, -5.0)	<0.001	886	-2.8 (-5.4, -0.2)	0.033	886	-2.8 (-5.4, -0.2)	0.033			
Systolic blood pressure	Women	610	-3.0 (-4.1, -1.8)	<0.001	1222	-2.7 (-3.8, -1.5)	<0.001	610	-5.9 (-7.6, -4.3)	<0.001	1222	-2.7 (-4.4, -1.0)	0.002	1222	-2.7 (-4.4, -1.0)	0.002			
	Men	565	-2.4 (-3.7, -1.1)	<0.001	884	-1.7 (-3.3, 0.0)	0.044	565	-5.4 (-7.2, -3.5)	<0.001	884	-4.4 (-6.4, -2.4)	<0.001	884	-4.4 (-6.4, -2.4)	<0.001			
Diastolic blood pressure	Women	610	-2.5 (-3.6, -1.4)	<0.001	1222	-3.6 (-4.8, -2.4)	<0.001	610	-6.0 (-7.5, -4.4)	<0.001	1222	-4.4 (-6.2, -2.7)	<0.001	1222	-4.4 (-6.2, -2.7)	<0.001			
	Men	565	-5.2 (-6.4, -4.0)	<0.001	884	-1.4 (-2.9, 0.1)	0.076	565	-9.0 (-10.6, -7.3)	<0.001	884	-4.7 (-6.6, -2.8)	<0.001	884	-4.7 (-6.6, -2.8)	<0.001			
Non-HDL cholesterol	Women	640	-2.2 (-3.4, -1.0)	<0.001	1210	-1.7 (-3.0, -0.5)	0.005	640	-2.1 (-3.9, -0.4)	0.02	1210	-2.6 (-4.3, -0.8)	0.004	1210	-2.6 (-4.3, -0.8)	0.004			
	Men	591	-2.3 (-3.6, -1.0)	<0.001	877	-0.4 (-1.9, 1.1)	0.58	591	-4.4 (-6.3, -2.6)	<0.001	877	-1.3 (-3.1, 0.6)	0.18	877	-1.3 (-3.1, 0.6)	0.18			
HDL cholesterol	Women	640	2.1 (1.0, 3.2)	<0.001	1210	1.7 (0.5, 2.9)	0.006	640	1.5 (-0.1, 3.1)	0.06	1210	2.1 (0.5, 3.8)	0.012	1210	2.1 (0.5, 3.8)	0.012			
	Men	591	3.5 (2.2, 4.7)	<0.001	879	2.1 (0.2, 3.9)	0.029	591	4.4 (2.6, 6.3)	<0.001	879	2.2 (-0.1, 4.4)	0.063	879	2.2 (-0.1, 4.4)	0.063			
Glomerular filtration rate	Women	495	-0.3 (-1.6, 1.1)	0.67	1210	0.2 (-1.2, 1.6)	0.79	495	0.5 (-1.4, 2.4)	0.60	1210	2.1 (0.1, 4.2)	0.04	1210	2.1 (0.1, 4.2)	0.04			
	Men	477	2.1 (0.6, 3.7)	0.006	877	1.0 (-0.8, 2.8)	0.27	477	3.5 (1.3, 5.7)	0.002	877	1.0 (-1.3, 3.2)	0.39	877	1.0 (-1.3, 3.2)	0.39			
Glucose	Women	640	-0.9 (-2.0, 0.2)	0.10	1210	-2.9 (-4.3, -1.6)	<0.001	640	-2.6 (-4.2, -1.0)	0.001	1210	-2.8 (-5.6, -0.1)	0.046	1210	-2.8 (-5.6, -0.1)	0.046			
	Men	591	-1.1 (-2.6, 0.4)	0.16	877	-1.7 (-3.6, -0.1)	0.042	591	-0.7 (-2.9, 1.5)	0.51	877	-2.9 (-5.0, -0.8)	0.006	877	-2.9 (-5.0, -0.8)	0.006			

* The average of septal and lateral e' tissue velocities was used as the dependent variable in the HyperGEN analyses.

[†] Values represent percent change in left ventricular function parameter per standard deviation increase in clinical variable. All regression analyses for associations with clinical variables (except for age) were adjusted for age, as was done in the study by Dalen et al.

SD = standard deviation; CI = confidence interval; HDL = high-density lipoprotein

Table 6

Replication of Known Associations of Conventional Echocardiographic Data with Speckle-Tracking Parameters in HyperGEN

Speckle-tracking echocardiography parameter	Conventional echocardiography parameter	Citation	Patients included in prior study	Prior study			HyperGEN		
				N	R	P value	N	R	P value
GCS, %	LV mass	Narayanan et al.	Normal, mild HTN	104	-0.28	<0.05	2147	-0.12	<0.001
GCS, %	Circumferential ESS	Narayanan et al.	Normal, mild HTN	104	-0.28	<0.01	2095	-0.22	<0.001
GCS, %	Relative wall thickness	Narayanan et al.	Mild HTN	52	0.05	NS	2147	0.04	0.045
LS, %	LV mass	Narayanan et al.	Mild HTN	52	-0.51	<0.001	2147	-0.23	<0.001
LS, %	Wall motion score index	Stanton et al.	Unselected patients	546	0.64	<0.001	2150	0.27	<0.001
LS, %	LV ejection fraction	Stanton et al.	Unselected patients	546	0.74	<0.001	2148	0.29	<0.001

GCS = global circumferential strain; LS = longitudinal strain; LV = left ventricular; ESS = end-systolic stress; HTN = hypertension; NS = not significant