Review Article

Adult echocardiographic nomograms: overview, critical review and creation of a software for automatic, fast and easy calculation of normal values

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Abstract: There is a crescent interest on normal adult echocardiographic values and the introduction of new deformation imaging and 3D parameters pose the issue of normative data. A multitude of nomograms has been recently published, however data are often fragmentary, difficult to find, and their strengths/limitations have been never evaluated. Aims: (I) to provide a review of current echocardiographic nomograms; (II) to generate a tool for easy and fast access to these data. A literature search was conducted accessing the National Library of Medicine using the keywords: 2D/3D echocardiography, strain, left/right ventricle, atrial, mitral/tricuspid valve, aorta, reference values/nomograms/normal values. Adding the following keywords, the results were further refined: range/intervals, myocardial velocity, strain rate and speckle tracking. Forty one published studies were included. Our study reveals that for several of 2D/3D parameters sufficient normative data exist, however, a few limitations still persist. For some basic parameters (i.e., mitral/tricuspid/pulmonary valves, great vessels) and for 3D valves data are scarce. There is a lack of studies evaluating ethnic differences. Data have been generally expressed as mean values normalised for gender and age instead of computing models incorporating different variables (age/gender/body sizes) to calculate z scores. To summarize results a software (*Echocardio-Normal Values*) who automatically calculate range of normality for a broad range of echocardiographic measurements according to age/gender/weight/height, has been generated. We provide an up-to-date and critical review of strengths/limitation of current adult echocardiographic nomograms. Furthermore we generated a software for automatic, easy and fast access to multiple echocardiographic normative data.

Keywords: 2D Doppler echocardiography; normal values; 3D echocardiography; strain

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Introduction

Quantification of cardiac dimensions is essential during the performance of echocardiography (1-5) and such measurements should be evaluated according to normative data (6-10). Echocardiographic nomograms are tools to estimate whether a cardiac dimension is within the range of normality or how far it diverges from it (6-10). In pediatric echocardiography, where cardiac dimensions significantly change with somatic growth, nomograms are essential and consolidate tools for the estimation of the severity of many congenital and acquired cardiac defects (6-10). In adults instead fixed rather than subject specific echocardiographic cut-off values have been generally employed for decades to grade disease severity and pose surgical indications (11,12). However, cardiac dimensions (13-37) and functional indexes (38-62) change with increasing age also in the adult population (63-87) and substantially differ according to gender and body size (88-96). Over the last few years (15-39), there has been a crescent call for patients specific rather than generic threshold values (40-64), leading multiple authors to publish echocardiographic normative data (65-85). In particular, four major multi-center studies (the Normal Reference Range for Echocardiography—NORRE-European, The Japanese Normal Values for Echocardiographic Measurement Project—JAMP, The Echocardiographic Measurements in Normal Chinese Adults—Eminca, and The Normal Echocardiographic Measurements in a Korean population—NORMAL-trials) are currently ongoing and normative data for many 2D and a few 3D parameters have been published (15-23,52). Contemporary, different centers addressed the need of having normative data for new parameters coming from 3D echocardiography (45-58) and deformation analysis (60-81). At present there is a big amount of echocardiographic normative data (15-39), but these data remain fragmentary and at times (40-64), difficult to find and time consuming (65-85). Not only current nomograms may difficult to access (15-39), but they may also result complicate to interpret, in view on non-linear variation of echo parameters with age (40-64), gender and body size (65-85). Furthermore nomograms coming from different sources (particularly those from different geographic areas) may generate different results. For instance, for a given male subject of 26 years, 65 kg weight and 168 cm height, LA atrial minimal diameters range of normalities may vary from to 41.8±5.2 (18) to 35.0±4.6 (16), up to 33.1±4.2 mm (22), according to the nomogram employed. Thus interpretation of nomograms requires knowledge of their accuracy and limitations (6-10), and similar analysis has never been performed so far.

The aim of this study was to review the published adult normative data for 2D and 3D echocardiography with the goal to provide an overview and to evaluate strengths and limitations of currently available data. A second aim was to provide a tool for an easy and fast access to a multitude of normative data coming from different sources, who may orientate the clinician in daily practice.

Search strategy

Studies were included after a systematic search in the National Library of Medicine (PubMed access to MEDLINE citations; http://www.ncbi.nlm.nih.gov/PubMed/). The search strategy included a combination of Medical Subject Headings and free text

Terms for the key concepts, such as: 2D and 3D echocardiography, strain, left ventricle (LV) and right ventricle (RV), atrial, mitral and tricuspid valve, aorta, reference values, and nomograms and normal values. Adding the following keywords, the results were further refined: range and intervals, myocardial velocity, strain rate and speckle tracking. In addition, we identified other potentially relevant publications using a manual search of references from all eligible studies and Review Articles, as well as from the Science Citation Index Expanded on the Web of Science.

Studies were searched from 2005 to 2017 using the above mentioned terms.

Two reviewers assessed all identified reports independently, and a consensus was reached for the final inclusion in the present study. Titles and abstracts of all articles identified by the search strategy were evaluated and excluded if (I) the studies included populations other than normal subjects (3 studies excluded), and (II) the reports were written in languages other than English (2 studies excluded), (III) studies with less than 100 healthy subjects at least considered very relevant for a lack of other more robust dataset (24 studies excluded), and (IV) for deformation analysis studies not performed with speckle tracking echocardiography (STE) (5 studies excluded).

Search results

One hundred and two publications were identified to be suitable for inclusion in this study. Of these, 34 were

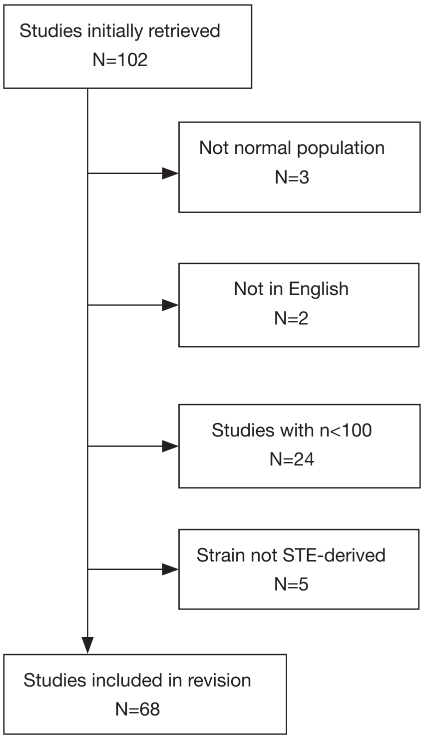


Figure 1 Studies included in the review. STE, speckle tracking echocardiography.

excluded on the basis of the criteria listed above, yielding 68 publications for analysis (*Figure 1*).

General aspects: how to build echocardiographic nomograms

When building an echocardiographic nomogram several aspects need to be taken into account. How to perform measurements in a standardised method? How to select healthy subjects (i.e., inclusion/exclusion criteria)? How many subjects are required to generate normative data with a sufficient statistical power and lately how to normalise and express normal values?

How to perform measurements

When building echocardiographic nomograms, a series of issues need to be faced (6,8-10). First it's important to decide how to perform the measurements (6,8-10). Guidelines for the quantification of 2D cardiac chambers (1,3) and functional indices (4,5), are well established. For 3D echocardiography, recommendations for chamber volumes quantification have recently become available (3) while guidelines for the 3D evaluation of cardiac valves mainly pertain to be an anatomical and functional assessment (without clear indication on basic quantification methods such as annulus measurements) (65). For strain analysis different methodologies may be employed (tissue Doppler echocardiography, 2D STE and, 3D echocardiography) (11-20), but a consensus document only exists for STE (and indications for RV and atrial strain analysis are limited) (65).

Inclusion and exclusion criteria

Definition of inclusion/exclusion criteria should be address accurately.

Only healthy subjects should be included, however health is a generic term (85,86) lacking of specific definition and inclusion criteria may change from a study to another. Our research highlighted how there was sufficient agreement on criteria of inclusion adopted by latest major studies (15-23,38,51,52,63). Hyperlipidemia, systemic hypertension, diabetes mellitus, lung disease, renal failure, liver failure, genetic syndrome, neuro-muscular disorders, abnormal electrocardiographic and/or echocardiographic findings, connective tissue disease, and poor image quality have been used as exclusion criteria in the majority of works (15-23,38,51,52,63). Pregnant or lactating women, athletes, and subjects addicted to alcohol were also excluded by a few authors (15,16,60), and some studies also evaluated smoking (15,21,38,82), anaemia and fever (15,16) as exclusion criteria. However, in some studies (15,19,38,43,52,54,63,82), inclusion criteria were well defined, in other sufficiently explained (20,21,24,30,50,52,61,67,70,74,76), while in few works the criteria were more generic (23,24,26,58,59,69,73).

Sample size

How many healthy subjects should be enrolled in another key point for the building of nomograms? Theoretically the sample size necessary to build a nomogram should be calculated by dividing the population into age-groups and assuming a minimum number of subjects for each of these age intervals (85-88). Assuming a normal distribution of the variables and estimating the population standard deviation (SD) at 0.5 (87-89) at least 80–120 subjects for every age group are necessary to provide a 95% confidence interval (CI) with a margin of error of 0.1 (74,75).

Thus assuming to divide the adult population into six age groups (i.e., 20–30, 30–40, 40–50, 50–60, 60–70, >70 years), as performed in the majority of the studies (15-17,21-23), at least 100 subjects for each study group should be enrolled (i.e., 600 in total). This number should be multiplied for the two genders (i.e., 1,200) and for multi-ethnic studies for the number race evaluated (i.e., for instance for 3 race Caucasian/Black/Asian; 600×2×3=3,600). Since almost all the studies consider a single race the threshold should be 1,400, and most of the nomograms currently available do not meet these criteria. Major studies had a sample size around 700 subjects (18-21,52), while only a few studies had a sample size >1,000 (15-17,26,35), (*Tables 1,2*). The widest study was the EMINCA study (15-17) with 1,394 healthy subjects (i.e., even above the target of 1,200 subjects). Some authors have tried to overcome the issue of sample size (65) by proposing meta-analytic works. However, the use of meta-analysis, although attractive, is questionable since heterogeneous data (collected in different ethnic population, of different ages and by using slightly different acquisition and quantification methods) are mixed together.

How to normalize and to express normalized data

Another issue when dealing with nomograms is how to normalise and how to express normalised data (6,8,9). Almost all studies presented data as mean values (plus or minus standard deviation) normalised by gender, age groups and at times indexed by body surface area (BSA) (15-23,34-36,38,50,58,59,61,90,91). A few studies used percentile (35,72,76-78,80) and one study employed z scores (41) that are commonly used in the pediatric age group. The relative scarce and inconstant relationship between parameters of body size (age, weight, BSA) producing low R2 (18,82) may explain the choice to employ mean values (plus or minus standard) instead of computing z scores, that theoretically should be preferred (6,8,9). Z score is a standard-bearer value that indicates by how many SDs a value is above or below the mean in a normally distributed population (i.e., z score of ±2 means that the measurement is 2 SDs above/below the mean). Z scores are better than dichotomous “normal or abnormal values” because they allow clinicians to appreciate the “magnitude of abnormality” (i.e., a z score of +4 indicates a severe dilatation), (6,8,9) Still, generation of suitable Z scores requires finding an appropriate model fitting the actual distribution of data and satisfying tight statistical assumptions, not always met in the published literature (9,10).

Confounders

Differences among age groups and gender have been widely studied (15-17,20-23). Influence of body size parameters (i.e., weight, height and body size) has been evaluated only in a few studies (50,81,82). Also the relevance of descent has been rarely investigated (68). All the authors have evaluated inter- and intra-observer variability and a good reproducibility emerged in most studies [with interclass correlation coefficients-(ICCs) vary from 0.6 to 0.9]. As expected, inter-observer variability was greater (i.e., ICC 0.3–0.9).

Nomograms for different echo measurements

Summary of the results

Generation of a software for automatic echocardiographic normal values calculation

To summarise data, major result of the studies selected were used to build a software who generates ranges of normality for echocardiographic parameters. *Echocardio-Normal Values* (97) is an application designed for mobile device with Android operating system published on Google Play store on 21 august 2017 by Infotel FTGM and currently available for free. It has been developed in JAVA language by using Android Studio 1.5.1, that is, Android’s official IDE developed and distributed by Google Inc. No external libraries were used. The same application was been also developed for desktop devices with Window, OSX e Linux operative systems by using a multi-platform development system. All rights are reserved and the application is distributed through specific installation packages, one for each kind of device. Reference tables and data for single profiles are stored in a SQLITE database that is included in the installation package. This software, for a given subject of a given age and gender, allows automatic calculation of normal values of echocardiographic measurements (i.e., 2D and functional indices, 3D data and strain values) and comparison among different sources. At the moment the software has been developed for operative systems desktop (Windows, OSX e Linux) and mobile (Android) (97) (*Figure 2*).

How to interpret data coming from different sources

Strength and limitations, similarities and differences, influence of age, gender and other confounders of current

Table 1 Major adult nomograms for echocardiography

Author/study	Study design	Population/race	Data normalization/ expression	Age groups (years)	Measurements
Part 1: 2D data					
NORRE (18), 2014 Europe	Multi-centers (22)	734 (320 M) 20–78 years, European	Mean SD divided by gender, age groups, indexed by BSA	20–40, 40–60, ≥60	LA diameters, area and volume in 2 and 4 ch, RA 4 ch diameters, area and volumes; M-mode: LV; LV volumes in 4 and 2 ch, RV 4 ch area and diameters; LVOT and RVOT (PLAX) (proximal and distal diameters)
JAMP (21), 2008 Japan	Multi-centers (17)	700 (383 M) 20–79 years, Japanese	Mean SD divided by gender, age groups, indexed by BSA	20–29, 30–39, 40–49, 50–59, 60–69, 70–79	LA diameters, area and volume PLAX and 4 ch, RA 4 ch diameters and area, M-mode LV; LV volume (4 ch, 2 ch), RV area and diameters (4 ch), Aorta (PLAX): annulus, sinuses, junction; Mitral inflow Pwd velocities (E, A, E/A, DT), mitral TDI lateral and septal (e', a', s'), Tei index
EMINCA (15), 2015 China	Multi-centers	1,394 (678 M) 18–79 years, Chinese	Mean SD divided by gender, age groups, indexed by BSA	18–29, 30–39, 40–49, 50–59, 60–69, 70–79	LA diameters, area and volume PLAX and 4 ch, RA: 4 ch diameters; M-mode: LV; LV volumes in 4 and 2 ch, RV 4 ch area and diameters; Aorta (PLAX): annulus, sinuses, ascending arch, diaphragm; Pulmonary annulus, MPA, LPA, RPA, LVOT and RVOT (PLAX)
Choi (22), 2015 Korea	Multi-centers (23)	1,003 (487 M) 20–79 years, Korean	Mean SD divided by gender, age groups, indexed by BSA	21–30, 31–40, 41–50, 51–60, 61–70, 71–80	LA diameters and volume PLAX and 4 ch, RA 4 ch diameters and area, M-mode: LV, LV volumes in 4 and 2 ch, RV 4 ch area and diameters; Aorta (PLAX): annulus, sinuses, junction MPA; LVOT and RVOT (PLAX) (proximal and distal diameters)
Lauer (32), 1995 USA	Single center	812 (288 M) 20–45 years, White European	Percentile charts for height divided for gender	–	M-mode LV and LA dimensions
Pritchett (80), 2003 USA	Single center	767 >45 years (355 M) 56.7±7.7 years	Percentiles for gender	–	LA dimensions and volume
Aurigemma (76), 2009 USA	Multi-centers	230 healthy aging (98 M) 76±5 years	Mean SD and percentiles for gender	–	LA dimensions and volume
Dwivedi (33), 2014 UK	Single center	480 >60 years (211 M), 70±7 years	Mean SD divided by gender	>60	MV: mitral annulus in systole and diastole in PLAX, PSAX, 4 ch and 2 ch views, tenting distance and area; TV: annulus at end systole and end diastole, tenting distance and area; RA, major and minor diameter; RV, longitudinal and mid-cavity diameter

Table 1 *(continued)*

Table 1 *(continued)*

Author/study	Study design	Population/race	Data normalization/ expression	Age groups (years)	Measurements
Mirea (36), Italy 2013	Single center	500 (269 M) 18–48 years	Mean SD divided by gender, age groups, indexed by BSA	<30, 30–39, 40–49, 50–59, 60–69	Aorta (PLAX) : annulus, sinuses, junction, ascending Ao, arch at the level of LSA
Vritz (35), France, Italy, USA 2014	Multi-centers	1,043 (503 M) 16–92 years	Mean SD and percentiles divided by gender, age groups, indexed by BSA	16–29, 30–39, 40–49, 50–59, 60	Aorta (PLAX): annulus, sinuses, junction, ascending Ao
Campens (41), USA 2014	Single center	849 (396 M) 1–85 years	Z score for gender		Aorta (PLAX): sinuses, ascending Ao
Vasan (34), 1995 USA	Single center	4,001 (1,849 M) 20–88 years	Mean SD and percentiles divided by gender, age groups, indexed by BSA	–	Aorta (PLAX): sinuses
Saura (17), 2017 (NORRE)	Multi-centers	704 (310 M) 46±13.5 years	Mean SD and percentiles divided by gender, age groups, indexed by BSA	<40, 40–59, >60	Aorta (PLAX): annulus, sinuses, junction, ascending Ao; short axis: sinuses
Functional indexes					
Dalen (26), 2010 Norway	Single center	1,266 (603 M) 47.8±13.6 years	Mean SD divided by gender, age groups	<40, 40–59, >60	Pwd Mitral Inflow: E, A, E/A, EDT, IVRT; pulmonary vein: S, D, S/D; LVOT: V max, VTI, pwTD and cTDI: mitral and tricuspid annulus: s' (pwTDI), s' (cTDI), e' (pwTDI), a' (pwTDI)
Biering-Sørensen (29), 2016 Denmark	Single center	954 (421 M) 20–93 years	Mean SD divided by Gender, Age groups	20–39, 40–59, >60	TDI M-mode: IVRT (ms), IVCT, ET, IVRT/ET, IVCT/ET, MPI
Choi (23), 2016 Korea	Multi-centers (23)	1,003 (487 M) 20–79 years, Korean	Mean SD divided by gender, age groups	21–30, 31–40, 41–50, 51–60, 61–70, 71–80	Pwd Mitral Inflow: E, A, E/A, EDT, IVRT; TDI: mitral and tricuspid annulus s', a', e'; pulmonary vein: S, D, Ar, LVOR and RVOT peak velocity and VTI
EMINCA (16), 2016 China	Multi-centers	1,394 (678 M) 18–79 years, Chinese	Mean SD divided by gender, age groups, indexed by BSA	18–29, 30–39, 40–49, 50–59, 60–69, 70–79	Pwd Mitral Inflow: E, A, E/A, EDT, IVRT, IVCT, LVET; TDI: mitral and tricuspid annulus s', a', e'; pulmonary vein: S, D, Ad, Ar-d, Ar–A; LVOT, Aortic valve, RVOT, pulmonary valve velocities
Munagala (30), 2003 USA	Single center	1,012 >45 years (46.3% men)	Mean SD divided by age groups	45–49, 50–54, 55–59, 60–64, 65, 69	Pwd Mitral Inflow: E, A, E/A, EDT, A duration; TDI: mitral annulus s', a', e'; pulmonary vein: S, D, Ar

Table 1 *(continued)*

Table 1 *(continued)*

Author/study	Study design	Population/race	Data normalization/ expression	Age groups (years)	Measurements
Part 2: 3D echo					
Bernard (95), 2016 Europe; NORRE	Multi-centers	440 (187 M) 19–75 years	Mean SD divided by gender, age groups, indexed by BS	20–40, 40–60, >60	3D LV volumes and mass; 3d GLS, GCS, GRS, GTS
Muraru (51), 2013 Italy	Single center	226 (18–76, 101 M) 18–76 years, Caucasian	Mean SD divided by gender, age groups, indexed by BSA	18–9, 40–59	3D LV volumes and mass
Chahal (50), 2013	Multi-centers	338 M, 161 F, 35–75 years, European Choort	Mean SD and percentiles divided by gender, age groups, indexed by BSA	35–44, 45–54, 55–64, 65–75	3 D LV volumes
Chahal (50), 2013	Multi-centers	290 M, 189 F, 35–75 years, Indian Asian Choort	As above	As above	As above
Fukuda (52), 2012 Japan	Multi-centers	410 (222 M) 20–69 years, Japanese	Mean SD divided by gender, age groups, indexed by BSA	20–9, 30–39, 40–49, 50–59, 60–69	3D LV volumes, 3D LA volumes
Aune (58,59), 2009 Noway	Single-center	166 (79 M) 29–79 years	Mean SD divided by gender, indexed by BSA	–	3D LV volumes, 3D RA and LA volume
Maffessanti (82), 2013 Italy	Multi-centers	507 (247 M) 18–90 years, Italian	Median- percentiles divided by gender, age groups, regression equation for age, gender, BSA	<30, 30–39, 40–49, 50–59, 60–69, >70	3D RV volumes
Muraru (63), 2014 Padua Italy	Single center	276 (118 M), 18–79 years	Percentiles global and divided into age groups indexed by BSA	18–29, 30–39, 40–49, 50–70, >70	3D LA volume
Mihăilă (47), 2014 Italy	Single center	224 (97 M) 18–76 years	Mean SD divided by gender, indexed by BSA	–	Mitral valve: 2d and 3d echo mitral annular geometry and dynamics
Sonne (45), 2009 Japan	Multi-centers	123 (68 M), 37±20 years	Mean SD divided by gender, indexed by BSA	–	Mitral valve: 2d and 3d MV and papillary apparatus parameters

Table 1 *(continued)*

Table 1 *(continued)*

Author/study	Study design	Population/race	Data normalization/ expression	Age groups (years)	Measurements
Part 3: strain values					
LV					
Yingchoncharoen (65), 2013	Metanalysis	2,597 (from 24 studies)	Mean values CI for the whole population	–	2D STE: Gε, GCε, GRε
Kleijn (61), 2015 USA	Multi-center (10 centers)	303 (156 M) 18–82 years, Europe/USA	Mean SD divided by gender and age groups, indexed by BSA	18–30, 31–40, 41–50, 51–60, 61–82	3d echo: GLε, GCε, GRε, Area ε
Kocabay (60), 2014 Romania	Single center	247 (98 M), 18–80 years, Caucasian	Mean SD global and divided for gender and age groups	18–35, 36–55, 56–80	2D STE: GLε, GCε, GRε, Regional longitudinal strain, Base and apical rotation, Twist
Marwick (67), 2009 Australia	Multi-center (3) Australia, Germany, USA	240 (105 M), 18–80 years	Mean SD (upper and lower limits) for the whole population	–	2DSTE: LV longitudinal strain global and segmental
Dalen (66), 2010 Norway	Single center	1,266 (603 M), 47.8±13.6 years	mean SD global and divided into gender	<40, 40–60, >60	2D STE: global and segmental Lε and Sε (infero-septum, antero-lateral, inferior, anterior, infero-lateral, antero-septum)
RV					
Muraru (72), 2016 Padua, Italy, RV	Single center	276 (55% women; age, 18–76 years	Percentiles global and divided into age groups indexed by BSA	18–29, 30–39, 40–49, 50–70, >70	2DSTE: right ventricle Lε
Forsha (73), 2014 Denmark	Single center	40 (16 M) 29 ±18.52 years	Mean sd (upper and lower limits) for the whole population		2DSTE: right ventricle Lε
Atrial					
Morris (68), 2014 Japan	Multi-center	377 (145 M) 36.1±12.7 years, Japanese and European	mean SD global and divided into age and gender groups	18–50, >51	LA: longitudinal strain and strain rate, ejection fraction, expansion fraction and volume index
Meel (69), 2017 USA	Single center	120 (60 M), 18–70 years, Black Americans	mean SD global and divided into age groups	18–29, 30–39, 40–49, 50–70	LA: volumes, function 2DSTE: LA longitudinal strain
Vianna-Pinton (74), 2009 USA	Single center	83 (32 M) 18–80 years	mean SD global	–	2DSTE: LA longitudinal strain

Table 1 *(continued)*

Table 1 *(continued)*

Author/study	Study design	Population/race	Data normalization/ expression	Age groups (years)	Measurements
Okamatsu (79), 2009 USA and Japan	Single center	140 (74 M), 3–79 years	mean SD global	–	2DSTE: LA longitudinal strain
Cameli (77), 2009 Italy	Single center	60 (41 M), 32.8±13.6 years	Percentiles for the whole population	–	2DSTE: LA longitudinal strain
Padeletti (78), 2012 Italy	Single center	84 (23 M), 19–71 years	Percentiles for the whole population	–	2DSTE: RA longitudinal strain
Moustafa (70), 2015 Canada	Single center	110 (50 M) 39±15 years	mean SD global	–	2DSTE: LA and RA longitudinal strain

ε, strain, A, mitral valve inflow PW doppler A velocity; a', late diastolic annular velocity; Ao, aorta; ch, chamber; Ar-d, time duration of right pulmonary vein reverse flow at atrial systole ad Ar; -A, time interval between Ar-d and Ad (A duration of A wave); CI, confidence interval; DT, deceleration time; D, PW doppler diastolic forward flow wave; GLε, global longitudinal strain; GCε, global circumferential strain; GRε, global radial strain; GTε, global tangential strain; IVCT, isovolumetric contraction time; IVRT, isovolumetric relaxation time; E, mitral valve inflow PW doppler E velocity; EDT, mitral E deceleration time velocity; ET, ejection time; LA, left atrium; LPA, left pulmonary artery; LV, left ventricle; LS, longitudinal strain; LSA, left subclavian artery; MPA, main pulmonary artery; MPI, myocardial performance index; MV, mitral valve; LVOT, left ventricular outflow tract; PLAX, parasternal long axis; PSAX, parasternal short axis view; pw, power Doppler; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle; RVOT, right ventricle outflow tract; S, PW doppler systolic forward flow; s' TDI, tissue doppler imaging; SR, strain rate; TV, tricuspid valve; V max, maximal velocity; VTI, velocity time integral; s', mitral/tricuspid valve annulus systolic velocity (TDI and Pwd); e', early diastolic annular velocity; mitral/tricuspid valve annulus earl diastolic velocity; 2DSTE, two-dimensional speckle tracking echocardiography.

adult echocardiographic nomograms will be now detailed for groups of parameters.

2D echocardiography

Robust nomograms, calculated on wide sample sizes for several major dimensional and functional 2D parameters have recently become available (15-23) coming from Europe (i.e., NORRE) (18) and Asia (i.e., JAMP, EMINCA) (15-17,20-23).

A dimensional indexes

Consistencies and discrepancies in the way to measure among authors

There was sufficient consistency in the way in which measurements have been performed. The LV mass was generally calculated by the equation for M-mode, while JAMP used the area length method (21). There was sufficient consistency also for left atrium (LA) and right atrium (RA) diameter measurements (15,18,21,22). LA volume was generally calculated by the biplane area length method while a few used the ellipsoid method (76), or both (22). Of interest, LA volumes calculated by the area length were significant higher than those calculated by the ellipsoid method (22). For the measurement of the aorta different techniques (inner edge *vs.* leading edge) and different timings in the cardiac cycle have been employed for measurements. Measurements obtained by using 2005 ASE criteria (37) (i.e., leading edge-to-leading edge technique in diastole) were higher in comparison with those by 2010 ASE pediatric guidelines (17,93) (i.e., systolic inner-inner diameters).

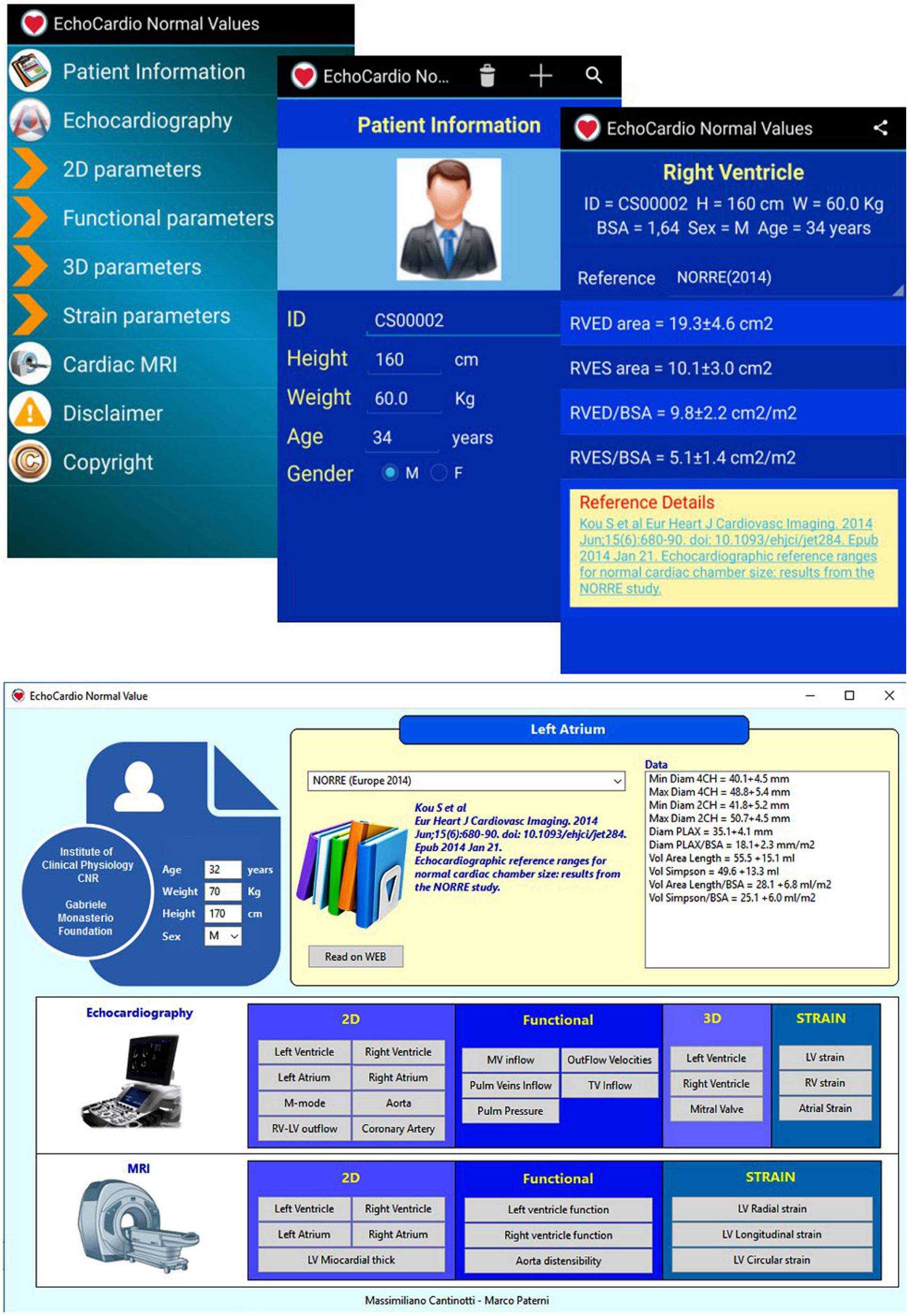
Correlation of cardiac measurements with age and gender and BSA and ethnic groups

All the studies showed significant relation of cardiac measurements with age, but results were somewhat discrepant. LV volumes have been shown to decrease with age (15,18,21,22), while the parietal thickness increased (15,21,22). A few studies reported an increase of left ventricular ejection fraction (LVEF) with age (15,18) while others found no variations (21,22). For LA diameters a positive correlation with age was reported by a few authors (15,21), while other showed age related variations only in female (22) or no significant variations (18). The absolute LA volume showed no age-related variations (21), while the indexed volume showed

Table 2 Major studies for 3D echocardiography normal values

Variables	Measure	Echo Machine	Software
Left ventricle			
Muraru (51,63,72) 2013, 2016	LV, RV, LA	GE Vivid E9 (GE health care Chalfont, UK); Philips Ie33 (Philips Health care, Best, The Netherlands)	(TomTec Imaging Systems, Unterschleissheim, Germany) and EchoPac BT13 (GE Vingmed),
Chahal (50) 2013	LV	Philips IE33 (Philips Health care, Best, The Netherlands)	Q-Lab 5, Philips Medical System
Fukuda (52) 2012	LV	Sonos 7,500 and Philips IE33 (Philips Medical Systems, Andover, AM, USA), Vivid 7 and Vivid E9 (GE Medical Systems, Milwaukee, WI, USa), SC2000 (Siemens Mountainview, CA, USA), Artida (Toshiba Medical System, Tokyo, Japan)	QLAb for Sonos 7500 and IE33, EchoPAc (Tomtec LV volume) for SC200 for Vivid 7 and Vivid E9, SC2000 Workplace (eSie LVA) for SC2000 and Advanced Cardiology Package for Artida.
Aune (58-59) 2010	LV, LA, RA	Philips IE33 (Philips Health care, Best, The Netherlands)	3DQlab, Philips
Bernard A (96) 2016	LV	Vivid E9 (GE Vingmed, Horten, Norway) and Philips IE33 (Philips Medical Systems, Andover, MA, USA)	TomTec 4D-RV Analysis, Unterschleissheim, Germany
Right ventricle			
Maffessanti (82) 2015	RV	Vivid E9 with 4V probe (BT 11; GE Vingmed, Horten, Norway) and Philips IE33 with X3-1 probe (Philips Medical Systems, Andover, MA, USA)	TomTec 4D-RV Analysis, Unterschleissheim, Germany
Mitral valve			
Mihaila (47) 2014	MV	GE Vivid E9 (GE health care Chalfont, UK); Philips Ie33 (Philips Health care, Best, The Netherlands) 4V and 6VT probes	4D autoLVQ, EchoPAC BT 12; GE Vingmed ultrasound and 4D-MV Assessment version 2.3; (Tomtec Imaging System, Unterschleissheim, Germany)
Sonne (45) 2009	MV	Sonos 7,500/(Philips, Andovber, MA, USA)	Real View, YD, Nara, Japan

LA, left atrium; MV, mitral valve; LV, left ventricle; RV, right ventricle.



ID CS00002
Height 160 cm
Weight 60.0 Kg
Age 34 years
Gender ● M ○ F

ID = CS00002 H = 160 cm W = 60.0 Kg
BSA = 1,64 Sex = M Age = 34 years

Reference NORRE(2014)

RVED area = 19.3±4.6 cm2
RVES area = 10.1±3.0 cm2
RVED/BSA = 9.8±2.2 cm2/m2
RVES/BSA = 5.1±1.4 cm2/m2

Reference Details
Kou S et al Eur Heart J Cardiovasc Imaging. 2014 Jun;15(6):680-90. doi: 10.1093/ehjci/jet284. Epub 2014 Jan 21. Echocardiographic reference ranges for normal cardiac chamber size: results from the NORRE study.

Age 32 years
Weight 70 Kg
Height 170 cm
Sex M

NORRE (Europe 2014)

Kou S et al
Eur Heart J Cardiovasc Imaging. 2014 Jun;15(6):680-90. doi: 10.1093/ehjci/jet284. Epub 2014 Jan 21.
Echocardiographic reference ranges for normal cardiac chamber size: results from the NORRE study.

Data
Min Diam 4CH = 40.1+4.5 mm
Max Diam 4CH = 48.8+5.4 mm
Min Diam 2CH = 41.8+5.2 mm
Max Diam 2CH = 50.7+4.5 mm
Diam PLAX = 35.1+4.1 mm
Diam PLAX/BSA = 18.1+2.3 mm/m2
Vol Area Length = 55.5 +15.1 ml
Vol Simpson = 49.6 +13.3 ml
Vol Area Length/BSA = 28.1 +6.8 ml/m2
Vol Simpson/BSA = 25.1 +6.0 ml/m2

Figure 2 Screen-shots of EchoCardio-Norm. This application, available for Android smart-phones and personal computers running Windows, OS X, and LINUX, allows for automatic calculation of a broad range echocardiographic normal values for a given subject of a given age and gender.

significant increase with age (15,22). RA diameters (15), RV long-axis diameter (15,22), and RV mass (15) increase with age, while data on the RV area were contrasting, with a study reporting a slight increase (21) and other a decrease of the RV area (18).

Some studies (15,18,22,27) showed significant relations of cardiac measurements with gender. All chambers diameters, volumes and the LV mass were higher in men (15,18,21,22), even after correction for BSA (18), as well as great arteries (15,22,27). BSA correction however mitigated RA diameters and RA volume differences among gender and eliminated differences in LA volume (18). Furthermore, indexed LV diameters were greater in women (22). Of interest functional data, including LVEF (18,22), LV sphericity index, RV fractional area change (FAC), and the tricuspid annular plane systolic excursion (TAPSE) (22) were generally higher in women. However, other studies reported no significant difference in LVEF (15).

Different among descendent have been noted. The ECHO_NORMAL study (25) revealed how LV end-diastolic volume, LV end-systolic volume, and LV stroke volume (SV) were highest in Europeans and lowest in South Asians. Similarly LV end-diastolic diameter, LV end-systolic diameter, LA diameters and volumes were higher for Europeans than in East Asian, South Asian, and African counterparts.

B functional indexes

Consistencies and discrepancies in the way to measure among authors

As for dimensional indices, there was sufficient consistency in the way to acquire and analyses Pulse Doppler and tissue Doppler velocities that were accomplished according to recent guidelines and recommendations (4,5).

Correlation of cardiac measurements with age and gender

For Doppler Flow mitral inflow parameters reproducible variations with age were noted (16,20,23,30,69). The E wave deceleration time (EDT) has been shown to increase with age, while the E and E/A decreased with age (17,20,23,30,69). For tissue Doppler imaging (TDI) velocities a significant decrease in LV and RV function with age was noted authors (16,20,23,26) with a few discordance in particular for mitral valve a' wave. While a few studies (16,23) described an increase with age, other reported a decrease (20,30). In contrast s' and e' decreased (16,23,30,69) and E/e increased with age (16,20,23,26). Similar variations were noted also for Doppler flow and TDI velocities measured at the tricuspid valve (16,23).

Pulsed Doppler velocities were higher in women (17,23,26) while EDT and isovolumic relaxation time (IVRT) were higher in men (23). No gender related difference emerged for the e' wave (16,23), while the s' and a' were detected to be higher in men (16,20,23), and the e/e' in women (16,23). Aortic and pulmonary valve velocities were found to be higher in men (16).

3D echocardiographic parameters

Despite advances normative data on 3D echocardiography remain limited. For LV and LA volumes (51,52,58,59,95) the sample size employed was relatively limited for all the studies ranging from 166 (58,59) to 440 (95) healthy subjects. There are sufficient data for 3D RV volumes, particularly those deriving from a study of Maffesanti and colleagues (82), including 507 healthy subjects. Data for the mitral valve are limited and different parameters have been evaluated by various authors (45,47). 3D data of aortic parameters are also very limited (54-56).

Consistencies and discrepancies in the way to measure among authors

Data on LV and LA volumes (51,52,58,59,95) have been published by using consistent methodologies. Data on the other measurements are too limited to make comparison.

Correlation of cardiac measurements with age and gender and BSA

Left ventricular 3D volumes decrease with age even after normalisation for BSA but in a few studies these correlations were only weak (50,52,59). The decrease in LV 3D volumes with age was counterbalanced by an augment in LVEF with advancing age (50,59,95) as occurred also for RV (82). Relationships of left atrial 3D volumes were opposite to the ones observed for the ventricles. In fact, LA 3D volumes increased with age (52,58,81) accompanied by a reduction of LAEF with age (58). LV volumes and mass were higher in men even after normalisation for BSA (51,52,95). The lower volumes in women were counterbalanced by the higher LVEF, however, the stroke volume remained higher in men (51,95). 3DE LA volumes were larger in men compared to women (52,58,81) and showed moderate positive correlations with body size parameters (i.e., height, weight, BSA, and body mass index; P<0.0001 for all) (81). LV volumes indexed by BSA was seen to be smaller in an Indian than a European population (50) while EF was similar between ethnicities. RV volume showed positive correlation with BSA, while EF decreases with an increasing BSA (82).

Comparison of 3D with 2D echocardiography and magnetic resonance imaging (MRI)

Comparison of measurements of atrial and ventricular volumes and functional indices by 3D versus 2D echocardiography provided contrasting results. Muraru *et al.* (81) showed that LA volumes measured by 3DE were 22% to 30% larger than the corresponding 2DE measures. The difference between 3DE and 2DE volumes was positively correlated with LA size measured by 3DE (r=0.36; P<0.0001), (81). LA total EF and passive EF measured by 3DE were also larger than 2DE. Conversely, expansion index was similar in this study (81). 2D echocardiography underestimated LV volumes (50,51) by an average of 2 and 4.7 mL/m^2 for LVED and LVES, respectively (50). Regarding functional indices, Muraru *et al.* (51) reported that LVEF stroke volume measured with 3D echocardiography was smaller than measured with 2D while in the study of Chalal *et al.* (50) a difference between 2D and 3D EF was very limited. No differences instead emerged among 2D and 3D data for the sphericity index (51), while LV mass was shown to be lower in 3D than 2D measurements (51). Only the works from the Padua group, provided a validation cohort for RV 3D volumes with MRI (51,82). Demonstrating that RV 3D volumes were lower than MRI measured data (82), confirming previous observations (3).

Deformation analysis

In the last years, normative data on new indices of STE data have become available for the LV (60,61,63,66,67), the RV (72,73), the LA (68-70,74,77,79), and the RA (70-78). Some of the most recent publications evaluated 3D STE parameters (61,72,95), while data on twist and untwist are still limited (60).

Despite a good representation of different geographic areas with data coming from Europe (60,61, 63,67,77,78,95), North America (63,67,69,70,74) and Asia (79), nomograms were constructed by using limited sample sizes with only two studies (61,68) having >300 subjects and one having 1266 subjects (66), the latter evaluated only LV longitudinal strain (ε). Data on LA ε are also extremely limited with only three studies having >100 subjects (71,84,94) and the widest population of 329 subjects (68). To overcome the lack of data, both for LVε (65) and for LA strain (65) meta-analytic works have been performed, despite the known limitations (6,10).

Consistencies and discrepancies in the way to measure among authors

Reproducible methodologies have been employed for LV 2D STE (60,61,66), while for atrial strain analysis differences emerged among authors (65). For longitudinal LV ε the 16 segments model excluding the apex has been generally used (60,61,66) while in some works whether the apex was excluded from calculation was not specified (67). The LA was analyzed by using a single projection (i.e., 4-chamber view, 6 segments scheme) (70,79), two projections (4- and 2-chamber views) (68,69,77,94), considering 12 segments (68,77,94), or 14 segments (69), or even by evaluating three projections (2- and 4-chamber view and long axis view, 15 segments scheme) (74). Notably, 2-chamber average peak atrial longitudinal ε (PALS) was significantly higher than in 4-chamber (P<0.0001) measurements, whereas there was no difference found between 2- and 4-chamber average time to peak longitudinal strain (P=0.93) (77).

Tacking quality was accomplished by using automated method (i.e., the automated QT score) (67,77) or more often subjectively (60,66,73,94). As summarised in *Table S1* different vendors have been used to acquire measurements, despite GE was mostly employed with few exception (68,79) and usually vendor specific software has been employed for data analysis with a few exceptions (66,70,95). Despite no specific recommendation for RV STE, guidelines for chamber quantification (3) recommend to calculate the peak value of 2D longitudinal strain (Lε) as an average over the three segments of RV free wall in 4-chamber view. However, some authors evaluated peak and mean strain in 18 segments over three projections (4-chamber, 3-chamber inflow and 3-chamber outflow) (73) while others compared methods evaluating peak and mean values of 6 and 3 segments analysis in 4-chamber view with and without apical exclusion (72).

Correlation of cardiac measurements with age, gender, BSA and heart rate (HR)

Data on age related differences in strain values are contrasting but a few reproducible patterns may be observed. Longitudinal LV strain trends to decrease with age measured both by 2D STE (61,66) and 3D STE (63) while circumferential strain increase (61,63,95). RV longitudinal strain age-related differences instead were small and not clinically relevant (72). Morris *et al.* (68) reported that LA ejection fraction, expansion fraction and strain were higher in younger, while systolic strain rate slightly higher in older adults. Furthermore, a decline of LA strain in the reservoir phase decrease with age was noted (68,69,79), while there were no differences seen in strain in the contractile phase.

Data on gender related differences of strain values are limited and inconsistent. Generally longitudinal and area strain (Aε) and strain rate (60,61,66) tend to be a bit higher in women while circumferential and radial strain showed no differences among gender (60,61). Overall men had lower 3D Lε, 3D Rε, and 3D Aε than women (51,95), although not in all age groups (51).

Regarding correlation with other confounders Marwick *et al.* (67) showed that weight, blood pressure (BP), Correlation of 2D and 3D LV strain with BP (50,51,60) have been demonstrated while HR correlated with 2D (50,60) but not 3D LV strain (51). For RV strain various demographic and cardiac parameters showed weak but significant correlations (72). No significant differences among gender emerged were noted in LA strain (65,68,69) and values were similar among Asian and European people (68). A decline of LA strain in the reservoir phase with increasing body size has been described in a recent meta-analysis evaluating major normative studies (65).

Conclusions

A great amount of adult echocardiographic nomograms, including data for 3D echocardiography and deformation indices, have recently become available. These nomograms present several strengths: cover almost all echocardiographic parameters, used consistent methodologies (i.e., inclusion/exclusion criteria, data acquisition and the way to perform measurements), and cover multiple ethnic groups. However, some limitations still remain. A few studies (particularly those on 3D and deformation indices) used a limited sample size, and there are also limited data for some basic cardiac structure (i.e., for mitral and tricuspid valve, both in 2D and 3D measurements as well as for the aortic valve 3D dimensions), data of black persons are very limited (69,96), and studies evaluating differences among ethnicity are lacking. Wider, comprehensive, multi-ethnic nomograms, which will fully evaluate old (i.e., 2D) and new parameters (i.e., 3D and deformation analysis parameters) are warranted.

Since the access to actual nomograms is often difficult and time consuming, we propose a software who automatic generate normative data for a given subject of a given age, weight, height and descent. This software should serve as a tool to orientate the clinician/sonographer in the difficult world of nomograms in a fast, accurate and reproducible way during routine clinical activity. Further researches are required to assess if a similar tool may allow to the clinician to save time and increase the diagnostic accuracy (as theoretically expected) (*Figure 2*).

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Footnote

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