Author's response to reviews

Title: WEB downloadable software for training in cardiovascular hemodynamics in the (3-D) stress echo lab

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Author's response to reviews: see over
Dear Rosa Sicari,

Please find attached the revised Manuscript:

“WEB downloadable software for training in cardiovascular hemodynamics in the (3-D) stress echo lab”

By:
Tonino Bombardini, Davide Cini, Giorgio Arpesella, Eugenio Picano

Thanks for the extremely useful and thoughtful review of our MS “WEB downloadable software for training in cardiovascular hemodynamics in the (3-D) stress echo lab”

In plain text, your comments; in italics, our response; in red, parts added to the revised manuscript (attached).

Reviewer: Rosa Sicari
Reviewer's report:
This is an interesting and well written manuscript addressing a timing and important issue such as the ability of a software to provide a full set of haemodynamic measurements during rest and stress echocardiography with the aid of 3D echo.

Thank you for your encouraging and helpful comments

There are only minor issues that authors should address:

1. Pg. 4 Systolic Blood Pressure: It is not clear what authors mean by: “Systolic blood pressure is obtained in the right arm with the patient instructed to grip the left support with the left hand”

We agree with you. We deleted the sentence and we rewrote it:

Systolic Blood Pressure (SBP, mmHg) and Diastolic blood pressure (DBP, mmHg). The blood pressure recording is made using a sphygmomanometer and the diaphragm of a standard stethoscope. The auscultatory pressure is obtained by inflating the cuff to a level approximately 30 mm Hg above the peak level of SBP and evaluating Korotkoff’s sounds. The systolic blood
pressure is recorded as the point where the first tapping sound occurs for 2 consecutive beats. The right and left brachial arterial systolic blood pressures are compared and discrepancies greater than 5 mm Hg are reported [12].

2. In order to improve the readability of the manuscript, authors should avoid abbreviations. Some of the parameters and their definition may be reported in table format.

We deleted abbreviations throughout the manuscript. Abbreviations are still present when parameters are defined and to better explain algebraic processes in tables and in CCtrainer electronic sheets. Please note that in the CCtrainer electronic sheets each definition/abbreviation can be expanded to a full description simply pointing the mouse cursor.

3. Pg. 15: authors should tone down the statement that:”qualitative and quantitative analyses of regional wall motion at rest and during stress become possible” which is not fully true.

To clarify this very important point, we deleted the sentence in the revised manuscript and we added a section, as follows:

Three-dimensional (3D) volumetric imaging has potential advantages in stress echocardiography, including the ability to provide an unlimited number of planes for analysis.

4. Please address in the study limitation that 3D echocardiography is still suboptimal for stress echocardiography due the low frame rate.

We added a paragraph commenting this potentially very important point

**Limitations of the study**

**3D stress echocardiography.** The success of imaging is high with pharmacologic stress but the feasibility is not established with exercise stress. The lower spatial and temporal resolution of 3D imaging and artifacts introduced by suboptimal subvolume integration are limitations of the current 3D technique. The ability to provide more planes for analysis has not been clearly shown to improve the accuracy of stress echocardiography. However, 3D imaging eliminates apical foreshortening, which is common with 2D imaging, and may improve detection of apical wall motion abnormalities. Development of automated image registration, quantitative analysis techniques, and single beat acquisition is needed to fully exploit the potential of 3D imaging in the stress laboratory [68, 69].

5. Some of the figure presented here have already been published on Cardiovascular Ultrasound. Some others are more suitable for a slide presentation than for a scientific paper.

Yes, thanks. We changed fig. 1, fig. 2, fig.3 fig.4, fig. 8 and we rewrote accordingly the figure’s captions. We agree with you that fig. 5, and fig. 6 are more suitable for a slide presentation than for a scientific paper but we think that concepts as arterial elastance, vascular resistance, arterial compliance and ventricular arterial coupling could be easier for the reader through this “cartoon” proposal.
Fig. 7 has already been published on Cardiovascular Ultrasound: however this figure is a standard explanation of the Wiggers cycle, previously Modified from Opie LH. Mechanisms of cardiac contraction and relaxation. In: Braunwald E, Zipes DP, Libby P, Bonow RO, eds. Heart Disease. 7th ed. WB Saunders Company 2005, Chap. 19:457–489, page 475.

We cited this in the figure’s caption.

Fig. 9, Fig. 10, Fig. 11 and Fig. 12 are presentations of the CCtrainer electronic sheets, according to “Manuscript sections for Technical notes articles”. Technical notes articles should present a new experimental or computational method, test or procedure. The method needs to have been well tested and ideally used in a way that proves its value. The description of the method and all details of the development and testing should be presented in the Results section.

6. When authors state that the first trial of the software is free, do they imply that the software is commercially available? Please clarify and provide details if it is so.

The CCTRAINER calculation program is completely free for use during the first month of operations. Algorithms and data sheets can be freely downloaded. Values and indexes are obtained automatically by software processing. After the first month, to continue using the program each user must be registered by the server administrator who assigns him/her an account and an exclusive memory area on the database server. Now time a user license could be purchased by bank transfer to the CNR.

Incassi da altre dipendenze IFC” Banca Nazionale del Lavoro
C/C: 218155
ABI: 1005
CAB: 03392
IBAN IT57S01005033920000000218155
Codice CIN: S
BIC Swift Code: BNLIITRR
Causale del bonifico: Cardiomonitor – IFC-CNR
We added the sentence:

A user license could be purchased by bank transfer to the CNR.

Page 1 of the WEB site http://cctrainer.ifc.cnr.it gives time and modalities of extending the time of program use. Individual waiver requests will be considered on a case-by-case basis and may be granted in cases of lack of funds.

Reviewer: Maurizio Galderisi
Reviewer’s report:
Very innovative proposal deriving from a group which always opens new tracks in the cardiologic community.

On behalf of all co-authors, I sincerely thank you for your most valuable comments.

In general, the manuscript is well written but paragraphs are often too long and could be simplified. The references are not always updated and appropriate. Some reference is lacking.

We changed the references according to your suggestions.
In addition, I would propose the possibility to differentiate two different software for different users: the first, simpler and shorter, for practical cardiologist, polarized on the most common hemodynamic parameters which can be utilized in the clinical practice. The second one, enriched by detailed quantitative information which can be useful for cardiologists involved in research programs. This could encourage a large use of the software.

According to your suggestions, the CCtrainer software is now set for different users: the practical cardiologist can fill only the first simple most common hemodynamic parameters which can be utilized in the clinical practice, i.e systolic and diastolic blood pressure, end systolic and diastolic LV volumes, heart rate: clicking on the results and the graph sheets buttons the Stroke volume, Cardiac Output, Mean Arterial Pressure, Pulse pressure, End-systolic pressure-volume determination, Arterial elastance, are calculated.

Furthermore, for teaching proposal, in the CCtrainer electronic sheets each definition/abbreviation can be expanded to a full description simply pointing the mouse cursor.

We added this in Fig. 9 and Fig. 10 captions:

Each definition/abbreviation can be expanded to a full description simply pointing the mouse cursor.

Cardiologists involved in research programs can completely fill rest and peak stress data linked to diastolic function, right ventricular and pulmonary artery function to have detailed quantitative information which can be useful for research protocols. To export data in excel or SPSS format is possible to shorten calculations and store data. We added in the Implementation section:

The exporting data in Excel or SPSS format is possible for shorten calculations and to store data.

Detailed concerns
The introduction is not very clear when the authors deals with 3D echocardiography: the meaning of the 3D advantage description in this part is not easy to understand for the readers.

To clarify this point we changed the introduction as follows:
Recent technological development and engineering refinements have allowed the application of real-time three-dimensional (RT3D) echocardiography in the routine clinical setting [1]. Because full-volume datasets obtained with RT3D echocardiography incorporate information on the entire left ventricle in four volumetric datasets, RT3D echocardiography has the potential to overcome many of the limitations encountered with two-dimensional echocardiography, mostly by eliminating the need for geometric modeling and the errors caused by the use of foreshortened views[2]. Three-dimensional (3D) volumetric imaging has potential advantages in stress echocardiography, including the ability to provides an accurate assessment of stroke volume, allowing derivation of a set of hemodynamic measures usually difficult or impossible to obtain with two-dimensional (2D) echocardiography [3, 4, 5, 6].

Page 4: 3D derived end-diastolic frame is not triggered to ECG in all 3D softwares.

You are right. We changed the sentence as follows:
LV End-Diastolic Volume (EDV, mL) is measured from the apical view by an experienced observer using 3D echo or by apical 4- and 2-chamber views using (Simpson’s rule) 2D echo. The frame captured at the R-wave in ECG in triggered software is considered to be the end-diastolic frame [13, 14]; or the end-diastolic volume is obtained from the LV volume curves as the maximum value.

Page 4: Deceleration time of E velocity should be added in relation with its recognized physio-pathologic and prognostic value.

A potential limitation of this study is the lack of information regarding Doppler indexes of diastolic function or dysfunction during stress. Doppler echocardiography is the preferred method for non-invasive diastolic function assessment. In current practice, most diastolic function indexes are derived by visual inspection of transmitral E- and A-waves. Deceleration time of E velocity should be added in relation with its recognized physio-pathologic and prognostic value. Average left ventricular (LV) chamber stiffness (ΔPavg/ΔVavg) is an important diastolic function index. An E-wave-based determination of ΔPavg/ΔVavg (Little WC, Ohno M, Kitzman DW, Thomas JD, Cheng CP. Circulation 92: 1933–1939, 1995) predicted that deceleration time (DT) determines stiffness as follows: ΔPavg/ΔVavg = N(Δ/DT)² (where N is constant). Other authors (Leonid Shmuylovich and Sándor J. Kovács Am J Physiol Heart Circ Physiol 292:2712-2720, 2007) found that deceleration time of E velocity is a function of both chamber stiffness and chamber relaxation viscoelasticity.

Mitral DT decreases slightly in normal individuals with exercise, but shortens >50 ms in patients with a marked elevation of filling pressures.

In the new Limitations of the study section, we added:

Doppler indexes of diastolic function. A potential limitation of this study is the lack of information regarding Doppler indexes of diastolic function or dysfunction during stress. Doppler echocardiography is the preferred method for non-invasive diastolic function assessment. In current practice, most diastolic function indexes are derived by visual inspection of transmitral E- and A-waves [70]. However during exercise E- and A-waves become difficult to separate and discern when the A-wave merges with the E-wave and covers more than two-thirds of the E-wave deceleration, which typically occurs at heart rate > 100 beats/min. Furthermore, details of E and A waves are not reliably discernable above 120 bpm due to noise and resolution limitations [71]. Despite diastolic heart failure currently accounts for more than 50% of all heart failure patients and stress echocardiography is useful for the evaluation of patients with dyspnoea of possible cardiac origin, difficulties exist in assessing variables that influence cardiac diastolic filling during exercise. The E/e´ ratio has been applied for that objective. In subjects with normal myocardial relaxation, E and e´ velocities increase proportionally, and the E/e´ ratio remains unchanged or is reduced. However, in patients with impaired myocardial relaxation, the increase in e´ with exercise is much less than that of mitral E velocity, such that the E/e´ ratio increases. In that regard, E/e´ was shown to relate significantly to LV filling pressures during exercise, when Doppler echocardiography was acquired simultaneously with cardiac catheterization [72, 73].

In cardiac patients, mitral E velocity increases with exertion and stays increased for a few minutes after the termination of exercise, whereas e´ velocity remains reduced at baseline, exercise, and recovery. Therefore, E and e´ velocities can be recorded after exercise, after 2D images have been obtained for wall motion analysis. However, the paucity of clinical data and the potential limitations in patients with regional LV dysfunction, mitral valve disease, and atrial fibrillation preclude recommendations for its routine clinical use at this time [54, 55].

The combination of a cutaneous operator independent force sensor and 3D stress echo allows a
highly feasible, fast and informative assessment of mitral infl ow rate, which could be impaired in
presence of diastolic dysfunction and provide insight on a novel form of diastolic stress
echocardiography [24].

Page 4: ASE and EAE have standardized the nomenclature of early diastolic of
mitral annulus as “e’” velocity; in addition ASE and EAE strongly encourage the
average of septal and lateral annulus values of e’ velocity.

You are right.

For the assessment of global LV diastolic function, it is recommended to acquire and measure
tissue Doppler signals at least at the septal and lateral sides of the mitral annulus and their average,
given the influence of regional function on these velocities and time intervals.

We changed the text accordingly to your suggestion:

**Tissue Doppler mitral annular tissue velocity e’ (cm/sec).** Mitral annular tissue velocity (e’,
cm/sec) is recorded using pulse-wave Doppler in the apical four-chamber view. It is recommended
to acquire and measure tissue Doppler signals at least at the septal and lateral sides of the mitral
annulus and their average, given the influence of regional function on these velocities and time
intervals. Mitral annular tissue velocity measurements are recorded at end-expiration during
ambient respiration [15].

Page 5: Is diastolic time corresponding to “diastolic filling time”?

Thank you for your thoughtful observation.

According to the physiological background, cardiological systole is demarcated by the interval
between the first and the second heart sounds, lasting from the first heart sound to the closure of the
aortic valve. The remainder of the cardiac cycle is automatically recorded as cardiological diastole
(A2 - M1 interval, filling phases included)

“Opie LH: Mechanisms of cardiac contraction and relaxation. In Heart Disease Volume 19. 7th
2005:457-489, page 475”

We changed the text accordingly:

A cutaneous operator independent force sensor, based on first heart and second heart sound
vibrations amplitude recording [22, 23], may be utilized to automatically quantify cardiological
systole and cardiological diastole duration [24] (Table 2). (Fig. 8).

<table>
<thead>
<tr>
<th>Table 2. Physiological vs cardiological systole and diastole</th>
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</thead>
<tbody>
<tr>
<td><strong>Physiological systole</strong></td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>Isovolumic contraction</td>
</tr>
</tbody>
</table>


Maximal ejection

Major part of isovolumic contraction*

Maximal ejection

Reduced ejection

**Physiological diastole**

Cardiological diastole

Reduced ejection

$A_2 - M_1$ interval (filling phases included)

Isovolumic relaxation

Filling phases

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*Physiological diastole* commences as calcium ions are taken up into the SR, so that the myocyte relaxation dominates over contraction and the LV pressure starts to fall as shown on the pressure-volume curve. In contrast, *cardiological systole* is demarcated by the interval between the first and the second heart sounds, lasting from the first heart sound to the closure of the aortic valve. The remainder of the cardiac cycle automatically becomes *cardiological diastole.*

*Obviously, cardiological diastole comprises diastolic filling time (filling phases), $A_2 – Mitral Opening interval (isovolumic relaxation) and the beginning of isovolumic contraction (mitral valve closure actually occurs about 20 milliseconds after the crossover of the pressures)*

We changed in the results section:

**Diastolic filling rate (mean, mL/m$^2$ *sec$^{-1}$)**

Diastolic mean filling rate [24] is calculated at rest and at peak stress as mitral filling volume (considered equivalent to the Stroke Volume index) divided by cardiological diastolic time (automatically sensor estimated) $\times$ 1,000

Diastolic Mean Filling Rate = (Stroke Volume index / Cardiological Diastolic Time) $\times$ 1,000

(mL/m$^2$ * sec$^{-1}$)

We added in the new *Limitations of the study* section:

**Diastolic Mean Filling Rate calculation.** For the calculation of the Diastolic Mean Filling Rate we utilized the automatically sensor estimated cardiological diastolic time that overestimates the diastolic filling time. In fact, the cardiological diastolic time comprises diastolic filling time, the $A_2 – Mitral Opening interval (isovolumic relaxation) and the beginning of isovolumic contraction (mitral valve closure occurs with a definite albeit short delay after the start of the LV contraction) (Table 2). This certainly introduces an approximation; nevertheless, any error is systematically distributed from rest to peak stress, probably not affecting the slope values of this novel form of diastolic stress echocardiography. Filling volume is the numerator and the cardiological diastolic time is the denominator of the equation. An overestimation of diastolic filling time (in the presence
of increased isovolumic relaxation time or of increased pre-ejection time) strengthens the clinical information given to a larger filling capacity at peak stress.

Page 4. Right atrial pressure: Please report reference of estimating right atrial pressure as described.

The reference of estimating right atrial pressure is Ref. # 27:


(Recommendations: for right atrial pressure calculation pag. 692, article references:

Page 5: Reference of methods for estimating pulmonary artery end-diastolic velocity is lacking.

We added the new # 28reference:

Page 9: Please, replace “E/E’ ratio” with “E/e’ ratio“

We replaced E/E’ ratio” with “E/e’ ratio“ throughout the manuscript

Page 10, line8: Ref # 54 and 55 are not appropriate.
Thank you for your observation:
We changed the Ref # 54 and 55 according to your suggestion with the new references:


Page 14, line 16: Ref 68 is not appropriate

We deleted the : Ref 68 and we changed it with the new #54 and #55 references:

Page 14, RV diastolic dysfunction: None utilizes deceleration time of tricuspid E velocity because is not reproducible. Also RV IVER is poorly used because of its large variability.

We agree with you, but we simply reported the new Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr.* 2010 Jul;23(7):685-713;

Page # 706

B. Measurement of RV Diastolic Function
See also Table 6 Diastolic function (Pag # 706)

Recommendations: Measurement of RV diastolic function should be considered in patients with suspected RV impairment as a marker of early or subtle RV dysfunction, or in patients with known RV impairment as a marker of poor prognosis. Transtricuspid E/A ratio, E/ E’ ratio, and RA size have been most validated and are the preferred measures(Table 6). Grading of RV diastolic dysfunction should be done as follows: tricuspid E/A ratio < 0.8 suggests impaired relaxation, a tricuspid E/A ratio of 0.8 to 2.1 with an E/E’ ratio > 6 or diastolic flow predominance in the hepatic veins suggests pseudonormal filling, and a tricuspid E/A ratio > 2.1 with a deceleration time < 120 ms suggests restrictive filling (as does late diastolic antegrade flow in the pulmonary artery). Further studies are warranted to validate the sensitivity and specificity and the prognostic implications of this classification.

In the opinion of this reviewer the figures are too many and Figure 9 and 10 have to be considered tables.

Please, see answer to reviewer 1, point 5.

Looking forward to hearing from you.
Sincerely

Tonino Bombardini, MD