SUBCLINICAL CARDIOVASCULAR DAMAGE IN CARDIOPULMONARY POLYMORBIDITY (REVIEW, PART 2)

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Abstract
Hypertension and chronic obstructive pulmonary disease are frequent comorbid conditions in the internal medicine and are subject to meaningful cooperation among physicians, cardiologists, and pulmonologists.
A combination of chronic obstructive pulmonary disease and hypertension presents certain diagnostic and therapeutic challenges. These conditions share common risk factors, similar clinical presentations and some common parts of pathogenesis. A problem of association between chronic obstructive pulmonary disease and hypertension may be currently discussed both as a simple combination of various clinical entities, and as chronic obstructive pulmonary disease resulting in development of factors contributing to hypertension. One way or another, either a simple combination, or a mutually aggravating syndrome, but we state there is a cardiorespiratory continuum where chronic obstructive pulmonary disease acts as a valid component of hypertension development, and vice versa. Thus, it seems to be relevant to study peculiarities of the structural and functional status of the cardiovascular system and microcirculation, systemic remodeling mechanisms, endothelial dysfunction and inflammation in presence of chronic obstructive pulmonary disease-associated hypertension. Problems of additional cardiovascular risk marker development, treatment efficiency assessment remain topical.
The use of electrocardiography and echocardiography with dopplerometry has been an important diagnostic principle of subclinical cardiovascular damage in presence of hypertension and chronic obstructive pulmonary disease comorbidity. Non-invasive imaging methods play a central part in diagnosis of subclinical target organ damage. Wide implementation thereof is based on high diagnostic accuracy, common availability, safety and relatively low price.

Key words: hypertension, chronic obstructive pulmonary disease, comorbidity, electrocardiography, echocardiography with dopplerometry.

Echocardiography
There are currently several options for echocardiographic studies available: Two-Dimensional Echocardiography, M-Mode, Doppler Echocardiography (Pulsed Wave – PW), High Pulse Repetition Frequency Doppler (HPRF), Continuous Wave (CW), Color Doppler, Color M-mode Doppler, Power Doppler, Color Tissue Velocity Imaging (Color TVI), Tissue Nonlinear Velocity Imaging, or C-Mode, Pulsed Wave Tissue Velocity Imaging, Tissue Tracking, Strain and Strain Rate, Vector Velocity Imaging or Vector Analysis of Endocardium Movement Velocity, Transesophageal Echocardiography, Stress Echocardiography, Three- and Four-Dimensional Cardiac Modelling, Intravascular Ultrasound, Contrast Echocardiography [1].

Echocardiographic signs of Right Atrial Hypertrophy
Up to day, only few studies have focused on the right atrial (RA) role in pathological conditions [2]. Right atrial dimensions are most often assessed through apical access in a four-chamber...
view. In this view, the RA area is assessed using planimetry [3]. The maximum distance along the RA long axis (longitudinal dimension) from the center of the tricuspid ring to the center of the upper wall of the AR "roof" is drawn parallel to the interatrial septum. A lesser transverse dimension through the middle of the RA is determined from the middle of the RA free lateral wall to the middle of the interatrial septum at right angle to the long axis. The RA area is outlined at the end of the ventricular systole from the lateral edge of the tricuspid ring to its septal edge, excluding an area between the valve leaflets and the fibrous ring along the AR endocardial edge [4].

**Echocardiographic signs of Right Ventricle Hypertrophy**

Unlike the RA, measuring the right ventricular (RV) dimensions requires using numerous echocardiographic views, including the parasternal view along the long and short axis view, RV inflow tract view, apical four-chamber and subcostal views. Change in the RV dimensions and function suggests increased pulmonary vascular resistance and load from the left heart chambers. Rapid increase in the RV afterload is known to present as the RV dilation, and a chronic one presents as concentric hypertrophy. In normal condition, the RV free wall thickness is less than 0.5 cm when measured both with M-mode, and with two-dimensional echocardiography. It is preferable to measure the RV wall from the subcostal view at a tricuspid valve chord level [5]. End-diastolic median and basal RV diameter measurement in the apical four-chamber view is a simple RV quantification method. Moreover, the RV longitudinal dimension may be measured in this view (*Table 2*).

**Echocardiographic signs of Left Atrium Hypertrophy**

Up to day, increase in the left atrial (LA) dimensions is known to be a marker both for severity and duration of diastolic dysfunction and pressure increase degree in the LA and is associated with development of adverse cardiovascular events [6]. Standard of the LA assessment is measurement of the anterior-posterior dimension with parasternal access to the LA long axis in M- or B-modes. In M-mode, it was measured from the anterior edge of the posterior aortic wall to the anterior edge of the LA posterior wall which, if normal, is 2.7–3.8 cm for women and 3.0–4.0 cm for men [6].

**Echocardiographic signs of Left Ventricle Hypertrophy**

The major diagnostic method for subclinical cardiovascular damages is assessment of the left ventricular (LV) dimensions, both linear dimensions, and LV myocardial mass (LVMM).

When echocardiographic findings are described, severity of damage is indicated as "minor", "moderate" or "major", allowing making conclusions about the damage intensity.

For linear and volumetric measurements of the LV (interventricular septum (IVS), posterior wall (PW), LV internal dimensions (end-systolic dimension [ESD] and end-diastolic dimension [EDD])), it is preferable to assess images in the parasternal view along the LV long axis.

It is recommended to measure the LV internal dimensions (ESD and EDD) and wall thickness at the LV minor axis level, at about mitral valve leaflet tips level. These linear dimensions may be measured both directly in the B-mode, and M-mode under B-mode control. An image made

**Table 1**

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Lower Normal Limit (95% CI)</th>
<th>Upper Normal Limit (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA Longitudinal Dimension (mm)</td>
<td>34 (32–36)</td>
<td>53 (51–55)</td>
</tr>
<tr>
<td>RA Transverse Dimension (mm)</td>
<td>26 (24–29)</td>
<td>44 (41–46)</td>
</tr>
<tr>
<td>RA End-Systolic Area (cm²)</td>
<td>10 (8–12)</td>
<td>18 (17–20)</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Lower Normal Limit (95% CI)</th>
<th>Upper Normal Limit (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal RV transverse dimension</td>
<td>24 (21–27)</td>
<td>42 (39–45)</td>
</tr>
<tr>
<td>Mean RV Transverse Dimension (mm)</td>
<td>20 (15–25)</td>
<td>35 (30–41)</td>
</tr>
<tr>
<td>RV Longitudinal Dimension (mm)</td>
<td>56 (50–61)</td>
<td>86 (80–91)</td>
</tr>
</tbody>
</table>
in the parasternal view along the short axis in B-mode or in M-mode under B-mode control may also be used when the view is positioned at the right angle to the IVS and LV PW. Measurements of the small axis in B-mode turn out to be smaller than measurements made in M-mode with the upper normal limit for EDD 5.2 cm vs 5.5 cm for M-mode. Normal LV EDD and ESD measurements make up 4.7±0.4 cm and 3.3±0.5 cm, respectively [7, 8]. LV internal dimension and IVS and PW thickness are measured at end-diastole and end-systole in a two-dimensional and M-modes [7].

Prolonged stable blood pressure increase and absence of adequate antihypertensive therapy result in the LV shape change. LV remodeling type, its geometric model are determined based on the LV myocardial mass (MM) and LV relative wall thickness (RWT). There are two popular methods of LVMM calculation: Penn and method, proposed by the American Society of Echocardiography (ASE).

According to the updated ASE recommendations to linear cardiac chamber measurement, the upper normal limit for LVMM is > 95 g/m² for women and > 115 g/m² for men [7].

There are two formulae for LV RWT calculation:
1) PW thickness × 2/diastolic LV diameter;
2) (IVS thickness + PW thickness)/diastolic LV diameter.

Patients with the concentric-type hypertrophy typically display high overall peripheral vascular resistance, subnormal systolic output and increased pulse pressure (PP) [9].

Patients with the eccentric-type hypertrophy typically display increased left ventricular cavity, high systolic output, relatively low overall peripheral vascular resistance with simultaneous relatively low PP. The latter is conditional upon arterial blood stream compliance in absence of significant vasospastic reactions. Increased venous tone or circulating blood volume are considered to be hemodynamic factor of LV eccentric hypertrophy development (e.g., in hypertensive disease patients) [9].

In concentric remodeling, LV wall thickness and myocardial mass are not increased, and decreased EDD and left ventricular cavity volume are the major remodeling signs.

There is an alternative LV geometry classification based on LVMM identification (along the vertical axis), LV volume (along the horizontal axis) and RWT (or LV mass to LV volume ratio) and includes eight types of ventricular remodeling [7, 8] (Table).

As the proposed classification suggests, a non-dilated ventricle has the following features: normal morphology, concentric remodeling/hypertrophy, confirmed LV hypertrophy and RWT > 0.42. A dilated, non-hypertrophied LV typically displays presence of eccentric remodeling with RWT < 0.32. A dilated LV with increased muscular thickness typically displays eccentric hypertrophy (RWT < 0.32), mixed hypertrophy (RWT > 0.42) or physiological hypertrophy (RWT 0.32-0.42).

EchoCG in COPD patients reveals pulmonary heart disease characterized by dilation of the right cardiac chambers, right ventricular wall hypertrophy, presence of pathological tricuspid regurgitation. All these signs suggest presence
of pulmonary hypertension. Paradoxical diastolic movement of the interventricular septum toward the left ventricle associated with pulmonary hypertension may be observed. However, a number of patients with chronic non-specific pulmonary conditions display only right ventricular wall hypertrophy, right atrial dilation, and pathological tricuspid regurgitation. The systolic function of the left and right ventricles may be normal or decreased. The diastolic function of the left ventricle typically has the first-type impairment. The diastolic function of the right ventricle may also have the first-type impairment, however, no clear correlation with the right ventricular systolic function impairment and pulmonary hypertension severity has not been determined so far. Studies are still conducted in this area [1].

Modern preventive and treatment strategy for the cardiopulmonary polymorbidity considers pathophysiological mechanisms of effects caused by risk factors early identification and elimination of which will contribute to significant improvement of prognosis. Therefore, it is very important to identify early markers of cardiopulmonary impairments which may help to determine a risk group at a preclinical level. Cardiovascular and pulmonary disease prevention is one of the highest priorities for the modern medicine [10].

**Functional markers of biventricular dysfunction**

Functional markers of both left and right ventricular dysfunction are widely used in addition to structural abnormalities to further stratify cardiovascular risk in patients with cardiopulmonary pathology.

### Table 4

**Description of Classic Remodeling Types**

<table>
<thead>
<tr>
<th>Type 1 – Normal Geometry</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMM ≤ 115 g/m² (men) or ≤ 95 g/m² (women)</td>
</tr>
<tr>
<td>LV RWT &lt; 0.42</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Type 2 – Concentric Remodeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMM ≤ 115 g/m² (men) or ≤ 95 g/m² (women)</td>
</tr>
<tr>
<td>LV RWT &gt; 0.42</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Type 3 – Concentric Hypertrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMM ≤ 115 g/m² (men) or ≤ 95 g/m² (women)</td>
</tr>
<tr>
<td>LV RWT &gt; 0.42</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type 4 – Eccentric Hypertrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMM ≤ 115 g/m² (men) or ≤ 95 g/m² (women)</td>
</tr>
<tr>
<td>LV RWT &lt; 0.42</td>
</tr>
</tbody>
</table>
**Left ventricular systolic function**

Estimation of functional state of the left ventricle should always include thorough evaluation of its systolic and diastolic function [11]. Markers that reflect left ventricular contractile capacity may be determined using a variety of imaging modalities, with sonographic techniques and MRI being the most widely used. Among these, transthoracic echocardiography is remaining the most cost-effective technique to be used with a purpose of screening of the patients, at the same time presenting an extensive set of parameters that may be acquired during a routine study.

Ejection fraction (EF) of the LV is the most widely used index of its global systolic function. EF prognostic role has been validated in a large number of prospective trials for patients with different types of myocardial impairment, with no data showing its limited accuracy or prognostic value in concomitant bronchopulmonary pathology [12, 13].

There is a strong data supporting the negative prognostic value of LVEF < 40% that has its reflection in the current guidelines on management of heart failure, with the values < 35% being even less favorable and therefore granting a more aggressive therapeutic approach to decrease the risk of sudden cardiac death [14]. The values of LVEF > 50% are considered normal, with a "grey zone" of 40 to 50% being defined as the mid-range ejection fraction (mLVEF); for these patients with heart failure, up to date there is no sufficient data to recommend any kind of outcome-modifying treatment but presence of mLVEF (even in a patient with no symptoms) should be perceived as a sign of subclinical myocardial impairment and therefore warrant further diagnostic search.

The pitfalls of using LVEF as a marker of systolic function include significant inter-observer variability [11] and technical limitations in case of suboptimal acoustic window; partially, these problems are being slowly overcome by introduction of the software for 2D and especially 3D automatic volumetry. LVEF measured by an MRI is considered the gold standard for left ventricular volumetry but remains too expensive to be used for screening purposes and lacks proper validation as a treatment-guiding modality (as all the studies justifying the cut-off values of the LVEF were performed using EchoCG) [15, 16].

The next widely used marker of LV global function is its global longitudinal strain (GLS), calculated directly using speckle tracking techniques or indirectly via tissue Doppler measurements [17, 18]. Being a more sensitive tool than EF, GLS tends to deteriorate earlier and therefore could be used for screening of subclinical myocardial impairment in a way similar to the one validated for patients undergoing chemotherapy [19], with an additional benefit of more precise estimation of local contractile abnormalities compared to traditional visual assessment. The pitfalls of GLS include lower availability in older scanners and significant inter-vendor variability [20] that limits the possibilities of comparing the results obtained by different scanners. The current guidelines estimate the lower range of normal values of the GLS as 17%, with additional remark regarding the need of using the same scanner in dynamic observation of a single patient; no data is available regarding the need of use of different cut-off value in bronchopulmonary pathology [21].

Other existing markers of LV systolic function, in general, do not have added diagnostic or prognostic value compared to EF and GLS, but there are two of them that may serve as a surrogate indices of LV global longitudinal contractility when assessment of GLS is technically impossible. Those are mitral annular peak systolic velocity (S’, derived in pulse-wave tissue Doppler mode) and excursion (MAPSE, M-mode derived and hence ready for acquisition on all available scanners). Lower normal limits for them are 7.0/10.0 cm/sec (for medial/lateral portions) and 16 mm (measured at lateral portion), appropriately. There is some data on negative prognostic value of both low MAPSE and S’ [14], both markers are easily obtainable and reproducible, and hence ready for use in dynamic observation of patients with a purpose of early detection of subclinical LV damage.

**Left ventricular diastolic function**

According to the current standards, evaluation of the LV diastolic filling should be routinely performed in every EchoCG study [21]. In patients with bronchopulmonary pathology, it is especially important in the context of differential diagnosis of post-capillary pulmonary hypertension due to impaired LV filling and pre-capillary PH being a result of pulmonary parenchymal and microvascular remodeling.

The current guidelines on the evaluating of LV diastolic filling [21] include a comprehensive algorithm for detecting and grading of diastolic dysfunction that is far from perfect due to a lot of patients being classified as having indeterminate diastolic filling, being widely...
debated and the description of which is not within this paper's purpose. Still, there is solid data on a set of functional markers that may be reliably used (with the exception of some specific settings) in most of the patients to detect and further observe the changes of LV diastolic function.

Thus, tissue Doppler-derived mitral annular peak early diastolic velocity (E') is an index of early diastolic relaxation of the myocardium of LV, with the cut-off values of 7.0 and 10.0 cm/sec for the medial and the lateral portions, appropriately. Late diastolic filling pressures is best correlated with the E/E' ratio (with E being a peak velocity of early diastolic transmitral flow). The current guidelines recommend to use the mean (medial/lateral) E’ value in the calculation and to take 13 [14] to 14 [21] as the upper limit of normal for the E/E’ ratio. Additional diastolic indices include late diastolic transmitral flow peak (A) and its annular equivalent (A’), E peak deceleration time (DTE), E/A ratio, isovolumetric relaxation time (IVRT) derived from transmitral flow or mitral annular motion, pulmonary veins flow pattern and some easy functional maneuvers that can be additionally used when estimating the LV filling state.

It cannot be stressed enough that the current approach is only able to estimate LV diastolic function in the setting of the left chambers morphology, with left ventricular hypertrophy supporting the presence of diastolic dysfunction in general, and left atrial enlargement > 34 ml/m² being one of the markers of elevated LV filling pressure [14, 21]. It is important to draw attention to the fact that the third index of elevated LVEDP, the peak tricuspid regurgitation velocity, should not be used in patients with bronchopulmonary disease, being a non-specific marker of pulmonary hypertension.

The diastolic indices presented above also have a wide set of limitations, the most frequently met of which are atrial fibrillation, calcification of the mitral annulus and significant mitral disease [21]. Still, even in these settings E' and E/E' can be used in a longitudinal monitoring of LV early and late diastolic function (given the stable state of mitral leaflets opening, stable severity of mitral regurgitation, and stable HR for atrial fibrillation).

Right ventricular systolic function
Proper evaluating of right ventricular performance should be and essential part of echocardiographic study in a patient with bronchopulmonary pathology, with right chambers being a target for adverse cardiac remodeling in pulmonary hypertension, and with a set of RV functional indices having been shown to have great clinical utility and prognostic value [22].

Tricuspid annular plane systolic excursion (TAPSE) is an easily obtainable with any scanner, highly reproducible parameter that mainly reflects the global longitudinal function of the RV but has shown good prognostic value and correlations with volumetric and planimetric estimates of RV contractility [23, 24]. According to the current consensus, TAPSE values < 16 [22] to 17 [11] mm should be interpreted as a sign of RV systolic dysfunction.

Peak systolic velocity of the tricuspid plane derived in a pulsed wave tissue Doppler mode at the lateral portion of tricuspid annulus (S') is another marker of the right ventricular global longitudinal contractility. The cut-off value for differentiating normal and abnormal function is 9.5 [25] to 10 cm/sec [22].

Both S' and TAPSE share the same innate limitations, with somewhat lower correlation to MRI- and scintigraphy-derived RV EF in states with regional wall motion abnormalities and inhomogeneous morphologic remodeling of the RV, including severe tricuspid regurgitation, acute pulmonary embolism, RV myocardial infarction, etc. [22].

Fractional area change (FAC) of the RV during systole, defined as (end-diastolic area – end-systolic area) / end-diastolic area × 100 (with the cut-off value of 35%), is up to date the most reliable and accurate index of RV global systolic performance that accounts for the possible regional motion abnormalities and correlates well with MRI-derived RV EF [26, 27]. The main major limitation of the FAC is that the technique of its obtaining is highly demanding to the quality of the RV endocardial tracing and hence the accuracy of measurements tends to dramatically drop in technically challenging cases, which is frequently essential in patients with pulmonary emphysema.

3D RV volumetric EF and RV free wall strain measurements are promising techniques that will probably help to overcome the limitations listed above in evaluating the RV systolic function [28, 29]. Still, up to date these techniques are not available in the majority of routinely used scanners, lack of validated cut-off values (which is of essential importance with regard to acknowledged inter-vendor variability [20], and therefore should be reserved mainly for research use.

Right ventricular diastolic function
Similar to LV function, changes in diastolic filling of the RV precede the decline of its contractility, and hence parameters reflecting RV
diastole could be used for longitudinal monitoring to detect early, subclinical changes in the RV function.

Unlike systolic function, where different shape and structure of the two ventricles lead to impossibility of use of some of the validated LV indices (e.g., 2D-derived EF) to adequately reflect the contractility of the RV, for thorough evaluating of diastolic function it is recommended to use mostly the same parameters as for LV.

As such, parameters like tricuspid E/A ratio (with a normal range of 0.8–2.1), E’ (lower reference value 8 cm/sec), E/E’ ratio (normal values < 6.0) can be monitored routinely, being the best validated and highly reproducible indices,

**Fig. 1.** Main parameters of the left ventricular global systolic function. A – LV ejection fraction using biplane simpson method; B – LV longitudinal strain in apical 4-chamber view. Adapted from [11]

**Fig. 2.** Main parameters of the left ventricular diastolic function. A – PW Doppler-derived transmitral flow velocities; B – PW tissue Doppler-derived mitral annular motion velocities; C – left atrial maximal volume using Simpson method; D – CW Doppler-derived peak tricuspid regurgitation velocity. Adapted from [11, 14]
with a possible estimation of E peak deceleration time and IVRT in challenging cases [22].

**Pulmonary artery pressures**

Being highly dependent not only on cardiac function but also on the state of pulmonary microcirculation that is being altered at advanced stages of most bronchopulmonary diseases, pulmonary artery pressure should not be taken as a reliable index of the global LV function.

At the same time, the information on RV afterload might be essential in understanding the mechanisms of RV structural remodeling and functional failure and hence should be routinely incorporated in every EchoCG report [22].

Of the indices used, systolic pulmonary artery pressure (SPAP) calculated as a sum of estimated right atrial pressure and RV systolic pressure by the peak tricuspid regurgitation speed (using modified Bernoulli equation) is the most reproducible and best validated index, with upper reference value of 35 mmHg [30, 31]. Indirect estimation of mean PA pressure (mPAP) using right ventricular outflow tract acceleration time might serve to outrule the pulmonary hypertension in technically challenging cases where tricuspid regurgitation jet is difficult to detect; the upper reference value for mPAP is 20 mmHg, with pressures over 25 mmHg being defined as pulmonary hypertension and 20–25 mmHg range falling into the "grey zone". These techniques [32] should not be taken as a substitute to SPAP measurement as their accuracy tends to dramatically decrease in high PA pressures.

Thus, detailed evaluation of the systolic function of both ventricles as well as LV diastolic filling should be an essential part of every EchoCG study, including those performed in patients with bronchopulmonary disease. With a purpose of early detection of subclinical functional alterations, additional monitoring of the RV diastolic indices might be advised in this category of patients.

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**Fig. 3.** Main parameters of the left ventricular global systolic function. A – RV fractional area change; B – tricuspid annular plane systolic excursion. Adapted from [11]
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