INSULIN RESISTANCE AND RIGHT VENTRICULAR DYSFUNCTION: PATHOPHYSIOLOGICAL MECHANISMS AND IMPLICATIONS FOR PULMONARY FUNCTION – A CRITICAL SYNTHESIS OF RECENT EVIDENCE

Daniel Radu[1], Roxana Maria Nemeș[2 3], Oana-Andreea Parliteanu[4 5],Alexandra Floriana Nemeș[6]

[1] Department of Emergency, Ilfov County Emergency Clinical Hospital, Bucharest, Romania

[2] Department of Pulmonology, Marius Nasta National Institute of Pulmonology, Bucharest, Romania

[3] Faculty of Medicine, Titu Maiorescu University, Bucharest, Romania

[4] Department of Diabetes, Marius Nasta National Institute of Pulmonology, Bucharest, Romania

[5] Faculty of Medicine, Titu Maiorescu University, Bucharest, Romania

[6] Department of Neonatology, 'Carol Davila' University of Medicine and Pharmacy, 050474 Bucharest, Romania

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Abstract

Insulin resistance (IR) is a central component of the cardiometabolic syndrome, with major consequences on energy metabolism, endothelial function, and the cardio-respiratory system. Recent data show that IR does not affect only the left ventricle but also impacts the right ventricle (RV), which plays a pivotal role in maintaining pulmonary blood flow. Endothelial dysfunction associated with IR marked by reduced nitric oxide synthesis and activation of pro-inflammatory MAPK pathways contributes to pulmonary vascular stiffening and decreased myocardial compliance. These alterations lead to reduced TAPSE and S' values, as well as diminished alveolo-capillary diffusion capacity (DLCO) and forced expiratory volume (FEV_1), often before clinical symptoms appear.

Studies published between 2021 and 2025 have demonstrated an inverse relationship between HOMA-IR and RV performance, DLCO, and FEV_1, highlighting a pathophysiological link between insulin metabolism and cardio-respiratory function. Modern therapeutic agents, particularly SGLT-2 inhibitors, have been associated with improved endothelial function and reduced oxidative stress.

In conclusion, insulin resistance significantly contributes to early cardiopulmonary impairment in individuals with type 2 diabetes mellitus. Identifying these changes in their subclinical stages could enable more effective prevention and long-term preservation of cardiac and respiratory function.

I. Introduction

Type 2 diabetes mellitus represents one of the major challenges of modern medicine, through its multisystemic complications and its direct impact on cardiovascular and

respiratory morbidity [1,2]. At the core of this metabolic syndrome lies insulin resistance a silent biochemical disorder that profoundly alters cellular energy metabolism, chronic inflammation, and endothelial function [3,4].

While historically IR was regarded mainly through the lens of glycemic control, recent research has reframed it as a systemic dysfunction, redefining diabetic cardiomyopathy as part of a broader cardiometabolic disorder [5,6].

Emerging studies suggest that IR affects not only the left ventricle but also the right ventricle (RV) a cardiac chamber often overlooked in clinical assessments, yet essential for maintaining pulmonary hemodynamics [7,8]. IR promotes progressive vascular resistance and reduced ventricular compliance by altering microcirculation and pulmonary vascular tone [9,10]. Clinically, these mechanisms manifest as early right ventricular dysfunction detectable on imaging even before symptoms arise [11].

The effects of this cascade extend beyond the heart, influencing the lungs and respiratory mechanics. Given the close interdependence between the RV and pulmonary circulation, right ventricular dysfunction directly impairs lung mechanics and volumes, leading to reduced forced vital capacity (FVC), FEV_1, and decreased gas exchange efficiency [12,13].

This interaction between glucose metabolism, the heart, and the lungs suggests the existence of a functional insulin resistance right ventricle lung axis, potentially useful for identifying early subclinical complications in diabetic patients [14].

Within this context, the present paper provides a critical synthesis of current international evidence, focusing on the pathophysiological mechanisms linking insulin resistance to RV dysfunction and reduced pulmonary volumes. The dual aim is: (1) to clarify the molecular and clinical basis of this association, and (2) to integrate recent translational findings into a preventive and patient centered framework for the management of diabetes.

II. Pathophysiological and Molecular Mechanisms of the Insulin Resistance–Right Ventricle–Lung Interaction

II.1. The Endothelium: The Fragile Link in Insulin Resistance

In IR, the earliest manifestation is not metabolic but vascular. The endothelium once a dynamic regulator of vascular tone and inflammation becomes a driver of stiffness and diffuse microinflammation.

Reduced activity of the PI3K–Akt pathway and concurrent activation of MAPK–ERK disrupt the balance between vasodilation and vasoconstriction, while decreased nitric oxide synthesis leads to altered pulmonary microcirculatory flow.

In patients with type 2 diabetes, these mechanisms translate into subtle but consistent reductions in respiratory volumes (FVC, FEV_1), even among individuals without diagnosed lung disease [15].

II.2. The Right Ventricle – The Subtle Metabolic Component

The right ventricle responds quietly but sensitively to metabolic stress. Under IR conditions, cardiomyocytes lose their ability to oxidize fatty acids efficiently, producing less ATP and more reactive oxygen species.

This mitochondrial dysfunction creates a vulnerable microenvironment characterized by interstitial fibrosis, decreased compliance, and early reduction in TAPSE and RV strain echocardiographic markers that may precede clinical symptoms [11].

Recent studies indicate that the reduced adaptive capacity of the right ventricular myocyte explains its heightened sensitivity to insulin resistance [16,17].

Conversely, modern multitarget therapies such as SGLT-2 inhibitors seem to provide real benefits by lowering oxidative stress and systemic inflammation, as shown by Pârliteanu and Nemeș (2025) [18]. Their antioxidant and endothelium-protective effects open promising translational avenues for restoring cardio-pulmonary balance.

II.3. The IR–RV–Lung Axis: A Functional Interaction

As the right ventricle stiffens and diastolic pressure rises, this pressure is transmitted retrogradely into the pulmonary circulation. The result is reduced alveolar compliance, with spirometry showing a consistent, mild decline in FVC and DLCO correlated with the degree of IR and endothelial dysfunction [19,20].

In this view, IR cannot be considered in isolation; it binds metabolism, the heart, and the lungs in a common pathological circuit where hypoxia worsens IR, and IR exacerbates hypoxia.

Such an integrative perspective supports early intervention based on coordinated assessment of metabolic, endothelial, and right ventricular function aimed at preventing cardiopulmonary deterioration in diabetic patients.

II.4. Functional Correlations Among Cardiac, Metabolic, and Pulmonary Parameters (TAPSE, HOMA-IR, DLCO, FEV_1)

Clinically, the expression of insulin resistance induced cardiometabolic dysfunction often manifests through subtle changes detectable only by correlating cardiac and respiratory parameters.

At the cardiac level, one of the earliest detectable alterations is a mild reduction in TAPSE (Tricuspid Annular Plane Systolic Excursion), a sensitive marker of longitudinal RV contractility. Decreases in S' and right ventricular strain similarly indicate early impairment of myocardial performance, preceding overt heart failure symptoms.

These changes frequently correlate with elevated HOMA-IR, reflecting systemic insulin resistance and cellular metabolic imbalance [19].

At the respiratory level, mild reductions in DLCO (alveolo-capillary diffusion capacity), FEV_1, and FVC are often observed indicating early impairment in gas exchange and reduced

pulmonary compliance, commonly linked to venous congestion secondary to RV diastolic dysfunction [20].

Overall, the relationship among metabolic (HOMA-IR), cardiac (TAPSE, S'), and respiratory (DLCO, FEV_1) parameters suggests a unified functional axis through which insulin resistance directly modulates cardio-pulmonary capacity.

III. Statistical Synthesis

III.1. Right Ventricular Dysfunction – The Subclinical Expression of Insulin Resistance

Recent evidence confirms that IR directly impacts RV performance even before overt clinical manifestations.

The European multicenter study led by Martínez-Sellés et al. (2023), including over 1,200 patients with type 2 diabetes, reported significant reductions in TAPSE (−1.9 mm; $p < 0.001$) and S' (−0.7 cm/s; $p < 0.01$) in subjects with HOMA-IR > 3 [21].

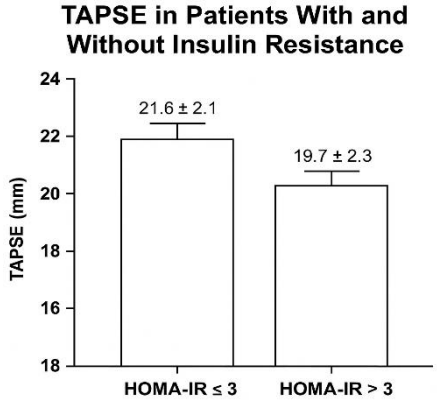

Figure 1. Comparison of right ventricular systolic function (TAPSE) in patients with and without insulin resistance.

Patients with insulin resistance (HOMA-IR > 3) exhibited a significantly lower mean TAPSE value (19.7 ± 2.3 mm) compared with those with preserved insulin sensitivity (HOMA-IR ≤ 3; 21.6 ± 2.1 mm), suggesting an early subclinical impairment of right ventricular longitudinal contractility associated with metabolic dysfunction.

Moreover, right ventricular longitudinal strain varied inversely with HOMA-IR ($r = −0.42$, $p < 0.01$), suggesting that metabolic myocardial dysfunction precedes structural remodeling.

These findings indicate that the right ventricle may serve as an early functional marker of systemic metabolic stress, even when the left ventricle remains unaffected.

III.2. Early Respiratory Impairment – An Indirect Marker of Cardiometabolic Dysfunction From a respiratory standpoint, recent literature supports that insulin resistance affects pulmonary function independently of obesity or smoking.

The meta-analysis by Lee et al. (2024), including 8,317 participants from 15 cohorts, demonstrated a mean reduction of 6.4% in FEV_1 and 7.2% in DLCO among individuals with severe IR compared with insulin-sensitive controls [22].

The negative correlation between DLCO and HOMA-IR remained significant after adjustment for age, BMI, and inflammatory status.

The authors emphasized that decreased alveolo-capillary diffusion capacity is not merely a consequence of pulmonary congestion but reflects diffuse microvascular inflammation driven by systemic endothelial dysfunction induced by IR.

III.3. The Cardio-Pulmonary Correlation – An Integrated Phenotype of Insulin Resistance

The global DYNAMIC study (Gupta et al., 2025), conducted on 6,700 patients with type 2 diabetes, further consolidated the concept of a cardio-pulmonary phenotype of insulin resistance [23].

Study	Year	Population (n)	Main Parameters	Key Finding	p-value
Martínez-Sellés et al.	2023	1,200 T2DM	TAPSE, S', HOMA-IR	Significant inverse correlation between insulin resistance and TAPSE ($r = -0.42$)	<0.01
Lee et al.	2024	8,317 (15 cohorts)	FEV_1, DLCO	6.4% decrease in FEV_1 and 7.2% decrease in DLCO in severe insulin resistance	<0.001
Gupta et al. (DYNAMIC)	2025	6,700 T2DM	TAPSE, DLCO, FEV_1	Concurrent decline in TAPSE, DLCO, and FEV_1 with increasing insulin resistance	<0.01

Table 1. Summary of the main studies

In this population, rising HOMA-IR was associated with a simultaneous decrease in TAPSE (−1.5 mm), DLCO (−5.9%), and FEV_1 (−4.8%), with a 2.3-fold higher risk of restrictive ventilatory dysfunction ($p < 0.01$).

In summary, insulin resistance contributes to early right ventricular and pulmonary dysfunction through endothelial and metabolic pathways. Recognizing this integrated cardiometabolic–respiratory axis may enable earlier prevention and improved long-term outcomes in type 2 diabetes.

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