



# Nimura lecture: why are you evaluating RV function in patients with pulmonary arterial hypertension?

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## Abstract

LV is a pressure-generating pump which endures pressure overload, while RV is a flow-generating pump intolerant of pressure overload. Therefore, RV pump function (but not RV myocardial contractility) can easily fail in face of severe pulmonary arterial hypertension (PH) because of increased afterload. Available indexes of RV function are load dependent and incapable of accurately reflecting RV myocardial contractility. Animal RV in which myocardium is damaged extensively by either soldering iron or coronary occlusion can work well without causing systemic congestion or decreased SV. In clinical settings, evaluation of pre-treatment RV function in patients with PH has limited value in predicting prognosis. Furthermore, in virtually all patients with PH after successful lung transplantation, RV function has been reported to improve indicating that deteriorated RV function in patients with PH is due to an increase in RV afterload, but not to decreased RV myocardial contractility. In view of these facts, evaluation of RV function seems hardly useful in patients with PH.

**Keywords** Pulmonary hypertension · RV function · Lung transplantation · Echocardiography

## Introduction

LV is a pressure-generating pump which endures pressure overload, while RV is a flow-generating pump intolerant of pressure overload [1]. In other words, RV function can easily decline in face of severe pulmonary arterial hypertension (PH). Although RV function is now “routinely” measured in patients with PH, it seems quite unclear how the results can be utilized in the management of PH patients. Therefore, I would like to think over the usefulness of evaluation of RV function in patients with PH in this article.

## Evaluation of LV function is extremely useful in clinical settings

Before discussing the meaning of evaluation of RV function, I would like to start with evaluation of LV function just for comparison. Needless to say, pumping function of the ventricle is determined by 4 factors: afterload, preload, myocardial contractility and heart rate. Emax measured as a slope of the line connecting end-systolic points of multiple LV pressure–volume loops represents LV myocardial contractility independent of either afterload or preload. In contrast, LV ejection fraction (EF) is a load-dependent index of LV pump function. Nevertheless, LV EF or even LV end-systolic size has been truly useful, for example, in deciding the optimum time for surgical intervention of patients with severe aortic regurgitation [2, 3].

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## Prognosis of idiopathic PH and Eisenmenger syndrome

It is of note that, in patients with Eisenmenger syndrome, RV is exposed to severe pulmonary hypertension but hardly fails because pressure, wall thickness and wall stress of RV and LV are equal from fetal life to adulthood. If a patient

survives the volume overload due to large left-to-right shunt during infancy, the RV is ready for a lifetime of functioning at systemic level pressure [4]. As a result, patients with Eisenmenger syndrome have better prognosis than those with acquired idiopathic PH whose RV easily dilates and fails [4, 5].

PH was regarded as a disease with poor prognosis in the 20th century. However, after the turn of the century, the advance in medical therapy for PH has dramatically improved the prognosis in both idiopathic PH and Eisenmenger syndrome [5–7]. Especially in patients with Eisenmenger syndrome, advanced medical therapy improved the 5-year mortality rate from 23 to <5%.

### RV is sensitive to pressure overload

Frequently cited results of Braunwald's dog experiments showed that RV is much more sensitive to afterload increase than LV [1, 8]. In face of pressure overload, RV dilates (not concentric hypertrophy, but eccentric hypertrophy) and uses preload reserve to maintain stroke volume. However, this preload reserve (Frank–Starling mechanism) easily deteriorates, decreases stroke volume and leads to RV failure. Because RV is dependent on preload reserve, RV EF or RV fractional area change (FAC) is not a competent index of RV function and it should always be evaluated along with RV end-diastolic volume (EDV) and stroke volume (SV). Namely,  $SV = RVEDV \times RVEF$ .

### Available indexes of RV function and their reliability

Frequently measured echocardiographic indexes of RV function are FAC (RV fractional area change), TAPSE (tricuspid annular plane systolic excursion), S' (peak systolic tricuspid annular velocity) and Doppler-derived index of RV myocardial performance (TEI index) [9]. FAC, TAPSE and S' have high specificity, but sensitivity and accuracy are low in detecting various kinds of cardiac diseases [10]. Furthermore, correlation with RV EF measured by magnetic resonance imaging (MRI) is acceptable only for FAC and poor in tricuspid annulus indexes such as TAPSE and S' because these indexes are affected deeply by dilatation of RV and dissonant directions of ultrasound beam and annular motion [11]. In my personal experience, a 32-year-old female patient with PH underwent lung transplantation which successfully reduced systolic PA pressure from over 87 mmHg to 26 mmHg as well as RV size. However, paradoxically "normal" values of pre-transplantation TAPSE (19–14 cm) and S' (13–9 cm/s) became "abnormal" after transplantation. In this particular case, TAPSE and S' are

totally useless in evaluating RV function. RV TEI index will be discussed later.

RV EF is not enough in evaluating RV function in patients with PH because of the reasons mentioned above. It is of note that RV pump failure in patients with PH is caused mostly by afterload increase and does not necessarily reflect diminished myocardial contractility.

### Can RV myocardial contractility be measured by pressure–volume (PV) loop analysis?

In LV, myocardial contractility can be estimated by PV loop analysis and the measured Emax is independent of preload and afterload. The PV loop of the normal RV differs significantly from that of the normal LV, in that RV loop has a triangular shape, and long RV ejection starts early during RV pressure rise and continues as RV pressure falls, making both isovolumic contraction phase and isovolumic relaxation phase obscure. These characteristics of RV PV loop make the end-systolic point and Emax less definable. Although RV PV loop in patients with PH becomes more rectangular and resembles that of LV, the measured Emax cannot be compared with that of normal subjects which is not obtainable for the above-mentioned reasons, and RV elastance analysis has limitations such as nonlinearity, variability in slope values and afterload dependency that cannot be ignored [8, 12, 13]. According to Prof. Motoaki Sugawara, LV is a pressure-generating pump and RV is a flow-generating pump. Intracardiac pressure is composed of static pressure and dynamic pressure, and cardiac catheter measures mainly static pressure. In LV, dynamic pressure (kinetic energy of blood flow) accounts for only 10% of total pressure while, in RV, dynamic pressure accounts for about 40% of the total pressure. Therefore, PL loop analysis works well with errors of about 10% for LV, but not for RV since pressure measurement errors of 40% seem unavoidable. In other words, RV is flow-generating pump in which flow energy cannot be ignored [14].

### Bypassed RV in Fontan circulation

In Fontan circulation, RV is bypassed and unused. Therefore, in the long term, a variety of complications of Fontan procedure have been reported mainly because RA and systemic veins are exposed directly to elevated pressure without interposed RV [15]. Nevertheless, the largest multicenter study reported 95% transplant-free survival over an average of 7 years of follow-up since enrollment in the Fontan study. Furthermore, QOL (the mean CHQ-PF50 physical summary score) of patients with Fontan circulation was indeed lower than those of healthy control subjects, but a large majority

of adolescent subjects continue to score within the normal range [16].

### Damaged RV myocardium in animal experiments

Several studies in which significant portion of RV free wall was destroyed by either soldering iron [17] or coronary artery occlusion [18, 19] reported that venous congestion did not occur, and stroke volume as well as LV function were maintained. The results of these studies indicate that RV with significantly damaged myocardial contractility still works well at least in short-term animal experiments.

### Prognosis of patients with PH

Prognosis of patients with PH can be discussed in 4 ways: (1) in the natural course, (2) with medical therapy of the 20th century, (3) with medical therapy of the 21st century and (4) with pulmonary transplantation. Before 1999, medical drugs available for PH were merely Ca antagonists and warfarin, while, after 2000, medical therapy has advanced strikingly, making prognosis of patients with pulmonary arterial hypertension as well as those with Eisenmenger syndrome strikingly better [4, 6, 20, 21]. Nevertheless, even the advanced medical therapy is not complete and prediction of response to therapy is helpful in clinical settings, with some patients showing a dramatic response and others requiring rapid escalation of therapy.

### Prognostic indicators for PH

ACCF/AHA 2009 expert consensus document recommends important prognostic indicators for PH including pericardial effusion, RV enlargement, RV dysfunction, RA enlargement, high RA pressure and low cardiac index by echocardiography or hemodynamic measurements, but this recommendation is not based on large-scale evidence [20]. In addition, the Document referred to Doppler RV TEI index (myocardial performance index), which appears to be predictive of an adverse outcome by multivariate regression analysis based on the data of 53 Mayo Clinic patients with PH. Only the Doppler RV TEI index and treatment with calcium blockers were independent predictors of prognosis [22]. However, it should be noted that RV TEI index can be related to all of the RV function, PA pressure and pulmonary vascular resistance as RV systolic time interval (STI: pre-ejection period over ejection time) and shows pseudonormalization in face of high RA pressure [23, 24]. Since this study was completed in

the era preceding the introduction of advanced PH therapies, new large-scale studies are anticipated.

In 2018, Weatherald reported a large-scale study [7]. Of 981 PH patients, a primary outcome (death or lung transplantation) occurred in 331 patients (33.7%) over a median follow-up duration of 2.8 years. Stroke volume (SV) index and RA pressure at first follow-up of right-sided heart catheterization after initial PH treatment were the variables that were independently associated with death or lung transplantation. Notably, in this latest large-scale study, follow-up data, but not baseline data, and SVI, but not CI, were predictive of prognosis. In other words, you cannot predict the prognosis unless you start medical therapy and recognize the efficacy of the therapy by measuring RA pressure or SV index.

### Universal normalization of RV function after successful lung transplantation

Unlike medical therapy, lung transplantation almost always yields striking decreases in pulmonary vascular resistance, pulmonary artery pressure and RV afterload. Severely decreased RV function may be considered to be a contraindication for lung transplantation, suggesting the necessity of heart–lung transplantation instead of lung-alone transplantation. On the contrary, a number of studies have shown that indexes of RV function such as RV size, RV free wall thickness, RV mass, RV EF, RV FAC, TAPSE, RV E/E' and RV strain improve in virtually all patients after successful lung transplantation [25–28]. Therefore, deteriorated RV function in patients with PH is due to an increase in RV afterload, but not to decreased RV myocardial contractility. RV dysfunction is not considered a primary determinant for lung transplantation eligibility.

### Conclusion

Available indexes of RV function are load dependent and incapable of reflecting RV myocardial contractility. Animal experiments showed that RV with significantly damaged myocardial contractility works well without causing systemic congestion or decreased SV. Not RV pump function, but RA pressure and SV index measured after initiation of medical therapy were reported to be useful in predicting prognosis. Furthermore, a number of studies have shown that indexes of RV function improve in virtually all patients after successful lung transplantation, indicating that deteriorated RV function in patients with PH is due to an increase in RV afterload, but not to decreased RV myocardial contractility. Therefore, you can evaluate RV function in patients with

PH if you want to, but you better ask yourself why you are evaluating RV function each time you do that.

Incidentally, it should be pointed out that PH patients with decreased LV function would tell us a whole different story.

## Another conclusion

I remember it used be like this: “I have found some good things beneficial to some patients who are suffering. So, I am going to write a paper to let them know the good things.” Quality was more important than quantity. Now, some but not all medical doctors are under the pressure of the “publish or perish” paradigm. In other words, they become obsessed with quantity rather than quality. This is simply unhealthy.

## Compliance with ethical standards

**Conflict of interest** Katsu Takenaka declares that he has no conflict of interest.

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