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Original Article

Pulmonary Hypertension Registry of Kerala (PROKERALA) – Rationale, design and methods

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ABSTRACT

Background: Pulmonary hypertension (PH) is a disease associated with a high morbidity and mortality. There is paucity of data regarding PH from the developing countries including India.

Idiopathic pulmonary arterial hypertension is the most important etiological factor in the western world, but PH secondary to rheumatic heart disease, chronic obstructive pulmonary disease and untreated congenital heart disease could well be the predominant causes in developing countries like India.

The main objective of the PROKERALA study – Pulmonary hypertension Registry Of Kerala is to collect data regarding the etiology, practice patterns and one-year outcomes of patients diagnosed to have PH.

Methods: The study is a hospital-based registry in the state of Kerala supported and funded by the Cardiological Society of India, Kerala Chapter. A total of 77 hospitals have agreed to participate in the registry. PH was defined as systolic pulmonary artery pressure derived by echocardiography of more than 50 mmHg (by tricuspid regurgitation jet) or mean PA pressure more than 25 mmHg obtained at cardiac catheterization.

A detailed questionnaire is administered which includes the demographic characteristics, risk factors, family history, ECG data, 6 minute walk test distance, chest X ray findings and echocardiographic data. Details of PH specific therapy and one-year follow-up data are collected.

From a preliminary survey in the region, we estimated that we will be able to collect 2000 cases over a period of one year.

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Pulmonary hypertension (PH) is characterized by increased pulmonary artery pressure and is associated with significant morbidity and mortality.[1] PH is defined by a mean pulmonary artery pressure of ≥25 mmHg at rest.[2]

1. Background

Epidemiological data regarding PH is not available from most of the developing world including India.[3] India is likely to have a huge burden of PH given the background of high prevalence of rheumatic heart disease, chronic obstructive pulmonary disease (COPD), and untreated congenital heart diseases (CHD). The burden of PH is likely to be different in the Indian context compared to the West, where idiopathic pulmonary arterial hypertension and PH related to left heart diseases predominate. In the developing world, it is postulated that PH secondary to rheumatic heart disease, COPD, and untreated CHD may predominate over primary PAH and PH related to left heart diseases.

The prevalence of the various ailments which can predispose to the development of PH, obtained from various community level studies in the first decade of the 21st century in India include: 1.5–2 per 1000 for rheumatic heart disease (all age groups),[4] 4.2/1000 for CHD (pediatric age group),[5] 4.5–10.5% for ischemic heart disease.[6] With this huge population having diseases which can predispose to PH, the burden of PH is likely to be very high in India.

Registries and surveys collect data rapidly and efficiently, allowing an analysis of a disease condition over a particular chronological interval. Registry data with its own limitations will provide a perspective of the problem in the community, for example – what are the etiologies leading to PH in the population.[7] Registry and survey data allow clinicians to compare their own practice with that of larger national or international reference populations. This provides an important stimulation for improvements in quality and consistency of practice. This will also help to form a database, which can help in studying the natural history of the disease.

There is renewed interest in PH due to the wide availability of pulmonary vasodilator drugs like Sildenafil, Tadalafil, Bosentan, and Ambrisentan which have all been found to be effective both in primary and in some cases of secondary PH. Over time, the cost of these drugs has also fallen making it more affordable to the majority of Indians who spend out of pocket. Registries also gather information regarding management patterns and outcomes of patients that can help guide the future strategies, which our physician community should follow.

Echocardiography-based registries in the developing world were found to be useful as in the case of the PAPUCO registry in Sub-Saharan Africa. The Pan African Pulmonary Hypertension Cohort study (PAPUCO) is an ongoing, prospective echocardiography-based observational cohort study; the objective is to describe the epidemiology and characteristics of PH in Sub-Saharan Africa.[8]

In this background, we have initiated a multi-center registry that allows organization of data regarding PH from different hospitals in Kerala.

2. Aim of the study

To initiate a registry of patients with PH from hospitals all over Kerala for one year from January 2015 to December 2015.

3. Primary objectives

- To know the pattern of clinical presentation of PH in Kerala.
- To assess the different etiologies.
- To understand the practice pattern regarding management of this condition among physicians in Kerala.
- To estimate the 6-month and one-year follow-up data.

4. Definitions

Patients with diagnosis of PH – defined as systolic pulmonary artery pressure (SPAP) derived by echocardiography more than 50 mmHg (by tricuspid regurgitation jet velocity method[9] – $4V^2$ + estimated right atrial pressure, where V is the TR jet velocity) in the absence of right ventricular outflow tract obstruction[2] or mean PA pressure more than 25 mmHg during cardiac catheterization – are being enrolled into the registry.[10]

It was decided to capture data of all etiologies of PH including PH associated with left heart diseases (Group 2 of the Revised WHO classification) for the registry. Given the chances of heterogeneity in the diagnostic methods in participating centers (most centers rely on echocardiography for diagnosis with only some centers likely to undertake diagnostic invasive cardiac catheterization based on the underlying etiology of PH), it was decided to include echocardiographic criteria with the SPAP of ≥50 mmHg (by estimation of the tricuspid regurgitation jet velocity) in the absence of right ventricular outflow obstruction. A higher diagnostic threshold was used to minimize false positives. Mukerjee et al. have shown that 97% of patients with an echocardiographically determined tricuspid gradient of >45 mmHg were found to have PH at catheterization, and they have suggested using a higher threshold to improve the diagnostic accuracy.[11]

We are using the WHO Classification (Danapoint 2008) to collect the information on the etiology of PH (Table 1).

5. Participating centers

Hospitals in Kerala with cardiologists, chest physicians, and general physicians treating patients with PH were contacted and requested to participate in the registry. A total of 65 hospitals across the state of Kerala have agreed to participate in the registry. The list of the hospitals and the principal investigators (PI) in those hospitals who are participating in the registry is attached in the Appendix I.

6. Administration and functioning

The physician enrolls the patient into the registry if the inclusion and exclusion criteria are satisfied and the patient is

Table 1 – WHO – Dana point classification of Pulmonary Hypertension (Table published with permission from Elsevier: Gérald Simonneau et al. *JACC* 2009;54:S43–S54).[12]

Group 1	Pulmonary artery hypertension	1.1 Idiopathic	
		1.2 Hereditary	1.2.1 BMPR2
			1.2.2 ALK-1, ENG, SMAD9, KCNK3.1
			1.2.3 Unknown
		1.3 Drug and toxin induced	
		1.4 Associated with	1.4.1 Connective tissue disease
			1.4.2 HIV infection
			1.4.3 Portal hypertension
			1.4.4 Congenital heart disease
			1.4.5 Schistosomiasis
			1.4.6 Chronic hemolytic anemia
		1.5 Persistent pulmonary hypertension of the newborn	
		1′ Pulmonary veno-occlusive disease and/or Pulmonary capillary hemangiomatosis	
Group 2	Pulmonary hypertension owing to left heart disease	2.1 Systolic dysfunction	
		2.2 Diastolic dysfunction	
		2.3 Valvular disease	
Group 3	Pulmonary hypertension owing to lung diseases and/or hypoxia	3.1 Chronic obstructive pulmonary disease	
		3.2 Interstitial lung disease	
		3.3 Others with mixed restrictive obstructive patterns	
		3.4 sleep disordered breathing	
		3.5 Alveolar hypoventilation disorders	
		3.6 Chronic exposure to high altitude	
		3.7 Developmental abnormalities	
Group 4	CTEPH Chronic Thromboembolic pulmonary hypertension (CTEPH)		
Group 5	Unclear, multifactorial	5.1 Hematological disorders – myeloproliferative disorders, splenectomy	
		5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis	
		5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders	
		5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis	

willing to sign the informed consent form (informed consent and the information sheet is attached – Appendix II). A simple questionnaire (study proforma) is being used to collect the data (see Appendix III). Characteristics collected include demographics, clinical characteristics such as mode of presentation, duration of symptoms, and echocardiographic data. The one-year follow-up data are also planned to be collected.

There will be two research coordinators stationed in the coordinating center – SCTIMST. They have been given training in data collection by the PI of the study. These research coordinators along with the local PI in each hospital imparted training to the echocardiography lab nurses and technicians in each participating center who collect the data. We had brought out a four-page instruction booklet describing how to fill the questionnaire (Appendix IV).

The data coordinator is visiting the sites periodically (monthly in the initial three months) and is collecting the filled questionnaire. Onsite checks for accuracy of the data and completeness of data are being done and the missing data are collected there itself. The deficiencies in data collection are pointed out and re-training is given if needed. This method was found successful in the case of Kerala ACS registry[13] and also the Trivandrum Heart Failure Registry,[14] which was conducted by the same team of investigators.

7. Investigators

The six PI are from three zones (two each from Central, South, and North regions) of Kerala. Each zonal coordinator is overseeing the data collection from hospitals in the region. The three co-coordinating centers are teaching hospitals, which are also referral hospitals, which is of advantage, since the physicians in a particular region may have a rapport with the coordinators.

8. Funding

Funding was obtained from the Kerala Chapter of the Cardiological Society of India (CSI-K). CSI-K has funded the Kerala ACS registry, the largest ACS registry in the country and also the CSI-KERALA CRP (CSIK – Cardiac Risk factor Profile study). The Kerala ACS registry was published in European

Heart Journal and the methods of the CRP study were published in Indian Heart Journal.[15]

9. Ethical clearance

The study was cleared by the respective Institutional Ethics Committees of each of the participating centers. For those hospitals which do not have their own IEC, the study proposals were cleared by the Independent IEC of the cardiological Society of India, Kerala Chapter.

10. Timelines

The study was initiated in January 2015. Some of the centers had delay in getting clearance from the respective Institutional Ethics committees, but the data collection in those centers will extend from a period of one year from the date of initiation. The follow-up also will extend accordingly in those centers. If we could collect accurate data, we are planning to convert this group of patients to a cohort and are also planning to follow them up for a longer period of time – 5 years or more.

11. Data management and analysis

Data analyses will be started after checking the data set for quality issues and missing variables. We will generate periodic listing of data queries for the sites to resolve data-related issues. A database lock will be employed to finalize the data set for statistical analyses. No statistical analyses will be conducted before the database lock and no modification of data will be allowed after the database lock. In order to present baseline characteristics, categorical variables will be presented as proportions with their 95% confidence interval. Distribution of continuous variables will be checked and normal distribution will be ensured before applying any parametric hypothesis testing. Continuous variables will be presented as means with standard deviation. If the continuous variables are not normally distributed, they will be presented as median with interquartile range. Both in-hospital and one-year mortality rate will be reported as a proportion (number of deaths/total registered patients) and per 1000 person-days of follow-up. Survival analyses will be employed to identify factors associated with mortality outcomes. Univariate survival models will be performed initially using Kaplan–Meier survival plots and groups will be compared using log rank tests. Any deviation from the proportional hazards assumption will be tested using log-minus-log plots. Later, if they satisfy the proportional hazard assumption, Cox proportional hazards models (Cox-PH) will be employed to evaluate potential multivariate adjusted risks of all-cause mortality. The multivariate model will include all relevant covariates/confounders based on existing literature and with a univariate $p < 0.20$. All analyses will be carried out using Stata 12 (StataCorp, College Station, TX, USA).

12. What this study is going to add to the literature

There are no data from the developing world including India on PH, even though 97% of the disease burden is from the developing world. This study will seek to bridge the gap of knowledge and will enable the physician and the research community to take a stock of the situation and streamline preventive and disease management strategies.

Conflicts of interest

The authors have none to declare.

Appendix A. Guidance to echocardiographic measurements.

A.1. *Right ventricular dimensions*

See Fig. 1

A.2. *Right ventricular systolic pressure*

See Fig. 2

A.3. *Pulmonary artery pressure – mean and diastolic*

See Fig. 3

A.4. *TAPSE*

TAPSE or tricuspid annular plane systolic excursion is a measure right ventricular function – the longitudinal function of the right ventricle. TAPSE is the distance of systolic excursion of the RV annulus along the longitudinal plane. It is obtained from a standard apical 4-chamber window by placing an M-mode cursor at the lateral tricuspid annulus and measuring the amount of longitudinal motion of the annulus at peak systole. The lower reference value for impaired RV systolic function of 16 mm (Fig. 4).

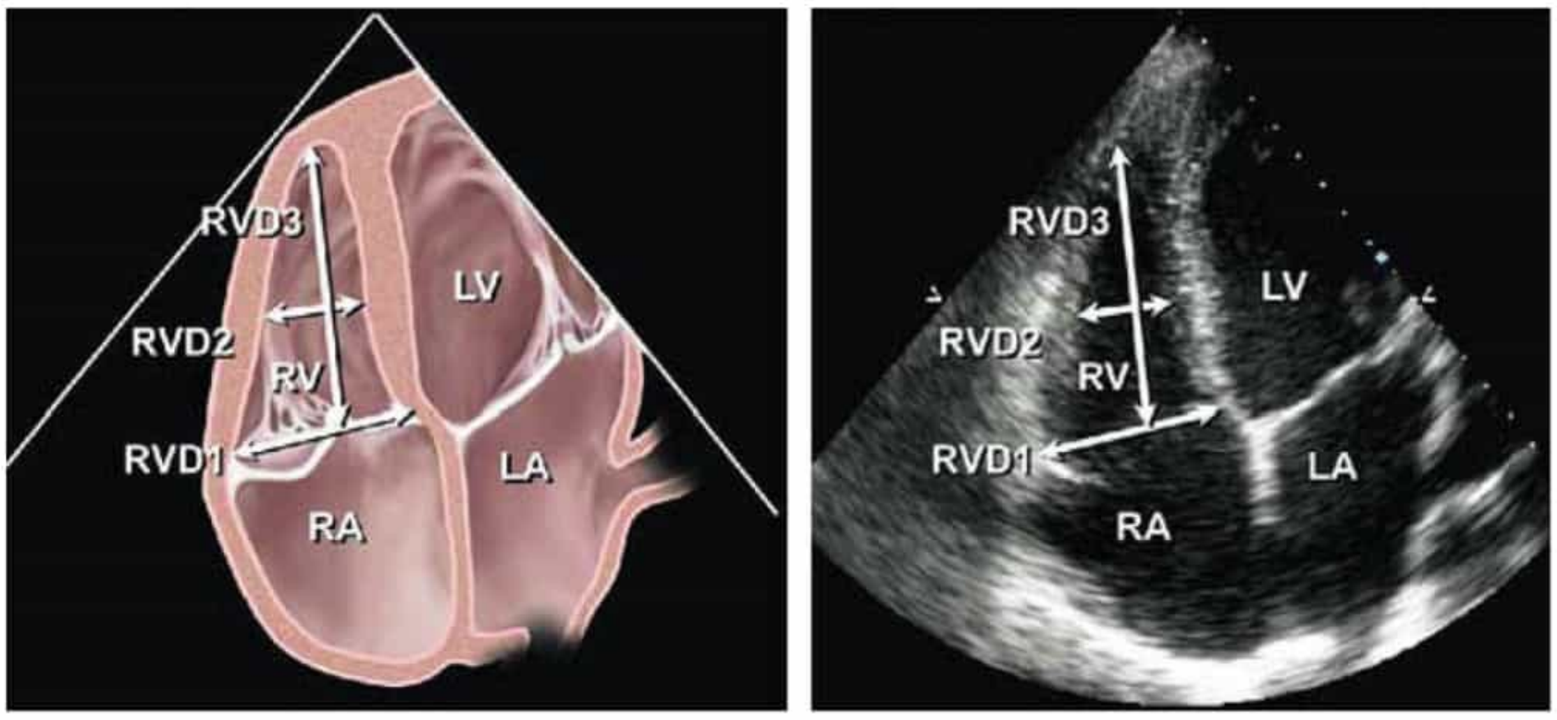

Fig. 1 – Measured in the apical 4-chamber view at end-diastole. The maximum diameter of the RV should be obtained without fore-shortening. RV diameter >42 mms at base (RVD1) or >35 mms at mid-RV (RVD2) and longitudinal RV dimension >86 mm (RVD3) indicates RV dilatation.
Rudski et al.,[9] image modified with permission.

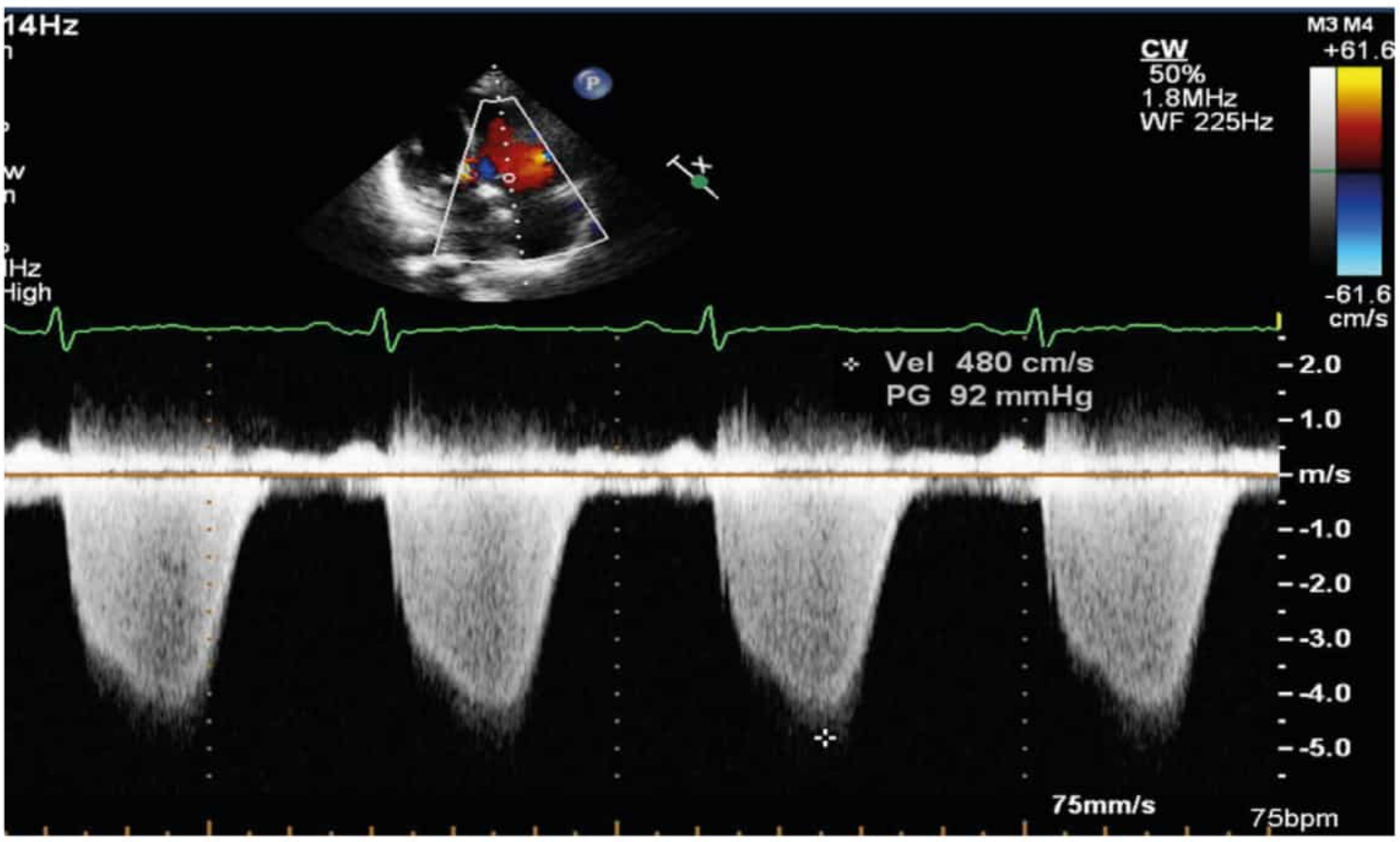

Fig. 2 – Doppler echocardiographic determination of systolic pulmonary artery pressure (SPAP). Spectral continuous-wave Doppler signal of tricuspid regurgitation (TR) jet is used to derive the SPAP. The TR jet velocity indicates the right ventricular (RV) – right atrial (RA) pressure gradient. The SPAP is derived as the sum of the estimated RA pressure (RAP) and the peak pressure gradient between the peak right ventricle and the right atrium, as estimated by application of the modified Bernoulli equation ($4\,V^2$ where V is the velocity of the TR jet) to peak velocity represented by the tricuspid regurgitation Doppler signal.[9] The RAP was estimated from the inferior vena cava diameter. If the IVC was ≤21 mm and the deep inspiratory collapse (''sniff test'') was >50%, RAP was estimated to be 3 mmHg; if the diameter was >21 mm and the collapse <50%, RAP was estimated as 15 mmHg; in intermediate cases, a value of 8 mmHg was assigned.[9] In this example, SPAP is estimated at 92 + central venous pressure, or 100 mmHg, if RAP is assumed to be 8 mmHg.

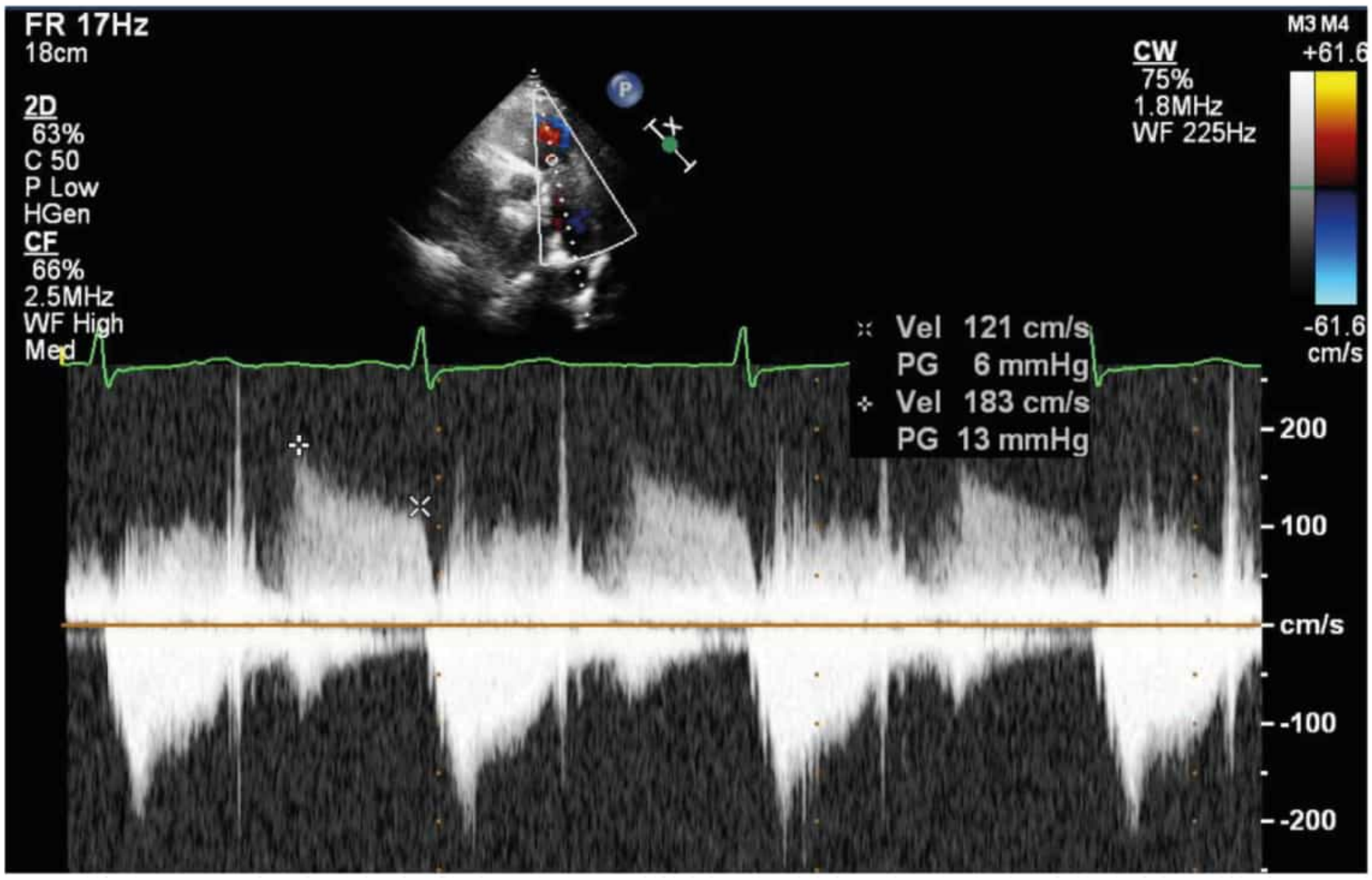

Fig. 3 – Doppler echocardiographic determination of pulmonary artery (PA) diastolic pressure (PADP) and mean PA pressure by continuous-wave Doppler signal of pulmonic regurgitation. Point 1 denotes the maximal pulmonary regurgitation (PR) velocity at the beginning of diastole. Mean PA pressure correlates with $4 \times (\text{peak PR velocity})^2$ + estimated RAP. In this example, PA mean pressure is 13 mmHg + right atrial pressure (RAP). Point 2 marks the PR velocity at end-diastole. PA diastolic pressure is correlated with $4 \times (\text{end PR velocity})^2$ + estimated RAP. In this example, PADP is 6 mmHg + RAP.

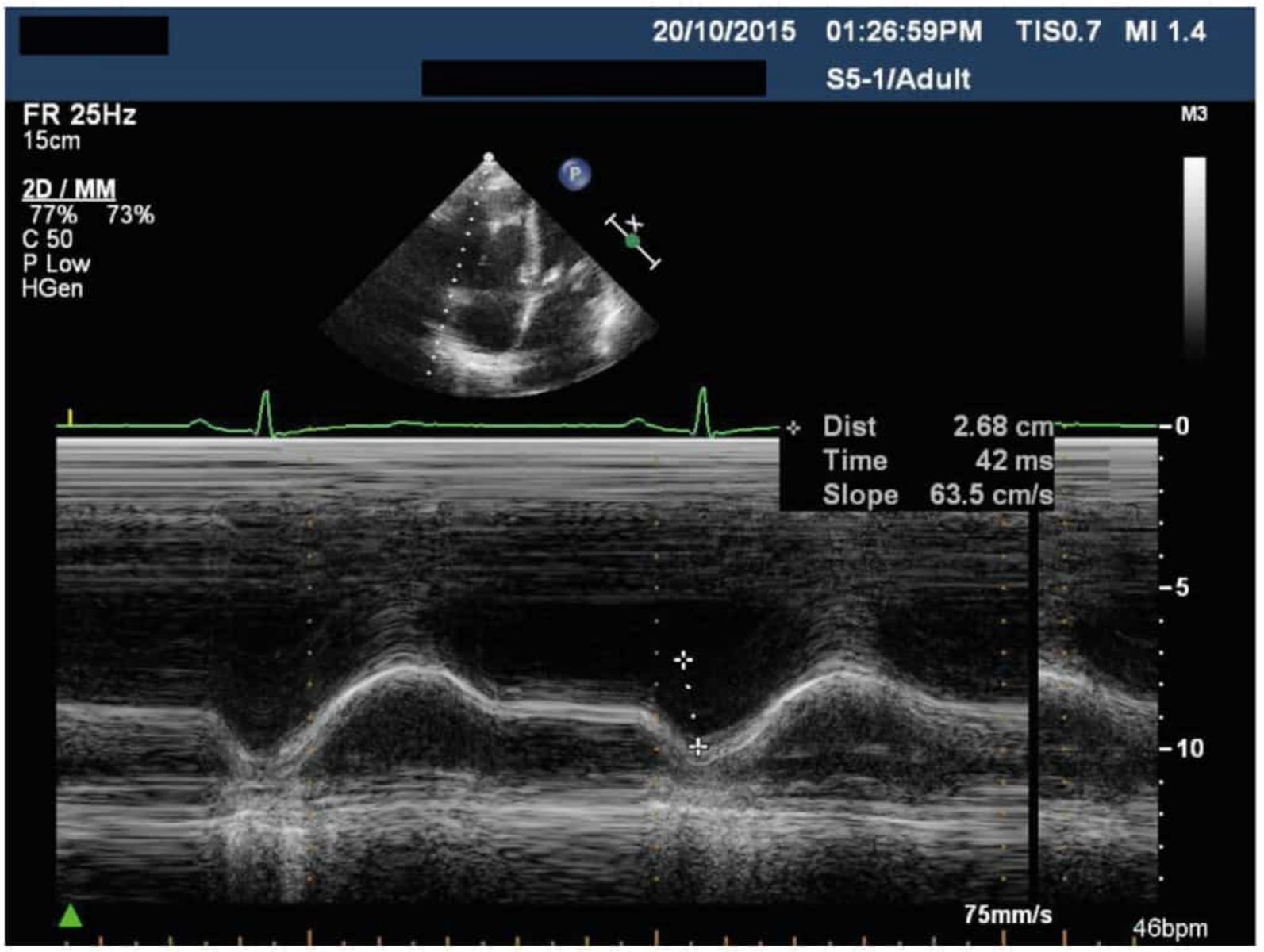

Fig. 4 – Measurement of TAPSE – in this example TAPSE is 26.8 mm.

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ihj.2015.12.010.

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