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Evaluation of the relationship between vitamin D deficiency and right and left ventricular systolic function in patients without coronary artery disease

Shahin Aliakbari[1], Maryam Shoja Safar[1], Mahdokht Rezaei[1], Abbas Allami[1], Hamidreza Javadi[1], Mohammad Mahdi Daei[1], Majid Hajikarimi[1], Ali Pazoki[1], and Kimia Rahimi Ardali[1]

[1]Qazvin University of Medical Sciences Qazvin Medical School

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Abstract

Background: Vitamin D deficiency is one of the most common nutritional deficiencies. Cardiovascular disease patients are also prone to this condition. Recently, a relationship between vitamin D deficiency and cardiovascular diseases has been suggested. This study aims to compare the relationship between ventricular systolic function and vitamin D deficiency. **Methods:** This study investigated patients without obvious coronary artery disease between 2020 and 2021. First, vitamin D levels were measured in the patients. Then, they were divided into two groups based on a 30 ng/dl cut-off point. All patients underwent echocardiography and ventricular systolic function parameters were evaluated and compared. **Results:** In this study, 27 patients with normal vitamin D levels and 47 patients with vitamin D deficiency entered the study. There was no significant difference in demographic variables and underlying diseases between these two groups. There was no significant difference between left ventricular (LV) systolic function parameters including ejection fraction (EF), and LV end-systolic/diastolic volume. No significant difference was also observed between right ventricular (RV) systolic function parameters including Tricuspid Annular Plane Systolic Excursion (TAPSE), RV fractional area change (RVFAC), Right ventricular systolic velocity (RVSM) in tissue Doppler echocardiography as well as RV diastolic parameters such as A, E, E´, deceleration time (DT), right atrial volume (RAVi) as a precursor of right ventricular systolic dysfunction groups. **Conclusion:** Based on the results of this study, there is no relationship between vitamin D levels and ventricular systolic dysfunction.

Evaluation of the relationship between vitamin D deficiency and right and left ventricular systolic function in patients without coronary artery disease

Maryam Shoja Safar, MD,[a] Mahdokht Rezaei, MD,[a] Abbas Allami, MD,[b] Hamidreza Javadi, MD,[a] Mohammad Mahdi Daei, MD,[a] Majid Hajikarimi, MD,[a] Ali Pazoki, MD,[a] Kimia Rahimi Ardali, MD,[c] , Shahin Aliakbari, MD,[c]

From :

a Department of Cardiology, Boali Hospital, Qazvin University of Medical Sciences, Qazvin, Iran

b Department of Infectious diseases, Boali Hospital, Qazvin University of Medical Sciences, Qazvin, Iran

c Student Research Committee, Qazvin University of Medical Sciences, Qazvin, Iran

Address for correspondence

Dr Mahdokht Rezaei

Iran ,Qazvin , Bo Ali hospital

Cardiology Department

ma.rezaei@qums.ac.ir

Tel: +9802833332930

Fax: +9802833326033

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we declare no conflict of interest

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Informed consent was collected from all patients

ethics approval statement :

the study was approved by the ethics committee of Qazvin University of Medical Sciences under the ethics code of IR.QUMS.REC.1399.104

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The data that support the findings of this study are available from the corresponding author,

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Abstract

Background: Vitamin D deficiency is one of the most common nutritional deficiencies. Cardiovascular disease patients are also prone to this condition. Recently, a relationship between vitamin D deficiency and cardiovascular diseases has been suggested. This study aims to compare the relationship between ventricular systolic function and vitamin D deficiency.

Methods: This study investigated patients without obvious coronary artery disease between 2020 and 2021. First, vitamin D levels were measured in the patients. Then, they were divided into two groups based on a 30 ng/dl cut-off point. All patients underwent echocardiography and ventricular systolic function parameters were evaluated and compared.

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Conclusion: Based on the results of this study, there is no relationship between vitamin D levels and ventricular systolic dysfunction.

keywords : Vitamin D, Systolic function, Diastolic function, Right ventricle, Left ventricle, Echocardiography

Background

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Vitamin D (Vit-D) deficiency is known to be an epidemic condition(1), and according to global estimates, more than 1 billion people are affected(1, 2). In Iran, the prevalence of Vit-D deficiency in men and women is 45.6% and 61.9%, respectively (3). The role of Vit-D is well-known in the homeostasis of calcium and phosphorus, but new findings show that Vit-D deficiency is involved in a variety of conditions, including hypertension, diabetes type I (4), fertility (5, 6), prevention of malignancies as well as autoimmune and infectious diseases (3, 7, 8).

In addition, studies show that the myocardium is an important target tissue for Vit-D (9). Three mechanisms are suggested for how Vit-D affects the myocardium; (1) direct suppression of renin gene expression, (2) presence of Vit-D receptors on myocyte membrane, and (3) hyperparathyroidism secondary to Vit-D deficiency may lead to myocardial hypertrophy (10-13). Low levels of 25-hydroxy Vit-D have been identified as an independent risk factor for overall and cardiovascular and cancerous mortality in patients referred for coronary angiography (14, 15). In addition, results from the Framingham Offspring Study showed that after a 5.4-year follow-up of patients without known cardiovascular disease, a low Vit-D level was independently associated with an increased risk of cardiovascular events(16).

In spite of the evidence linking Vit-D deficiency with heart function, objective evidence such as echocardiographic findings has yet to be adequately investigated. The previous studies' results showed different and even contradictory results (18-21). Previous studies have mainly investigated the relationship between Vit-D status and pulmonary hypertension, some of them showed that patients with pulmonary hypertension have lower serum Vit-D levels than healthy individuals (31, 32), and to the best of our knowledge, this is the first to examine the relationship between Vit-D status and both left and right ventricular function. Therefore, the aim of this study is to investigate the relationship between serum 25-hydroxy Vit-D level and systolic functional parameters based on the echocardiographic systolic heart function parameters evaluation.

Methods

Study population

This study was conducted as a cross-sectional study between 2019 and 2020. The studied population included patients without known coronary artery disease (CAD) or with minimal CAD who were referred to Bu-Ali Sina Hospital in Qazvin for angiography.

After determining the sample size, convenient sampling was performed and the patients were divided into two groups: Vit-D deficient (Vit-D<30 ng/dl) and Vit-D sufficient (Vit-D[?]30 ng/dl) (22). The considered exclusion criteria were: severe coronary artery disease, history of structural heart disease (Congenital heart disease or valvular heart disease), arrhythmia or history of atrial fibrillation, use of medicines that affect the electrical conduction of the heart, use of Vit-D supplement in the past month, cerebrovascular disease, renal failure or secondary hypertension, abnormal thyroid tests, and immunodeficiency. patients' histories including BMI, BSA, SBP, DBP, underlying diseases such as dyslipidemia and diabetes and drug histories of patients were documented.

The study did not cost patients extra, and informed consent was obtained from all patients. The study was conducted in accordance with the Helsinki Declaration and the study was approved by the ethics committee of Qazvin University of Medical Sciences under the ethics code of IR.QUMS.REC.1399.104

Standard Echocardiography

All samples underwent transthoracic echocardiography performed by an echocardiography fellow at the time of angiography, followed by a recording of the parameters of ventricular systolic and diastolic function.

Standard echocardiography was performed using Philips Affiniti 50 Ultrasound Machine (Philips Healthcare, Andover, MA, USA) in a left lateral decubitus position. The measurements were performed according to the American Echocardiographic Association guideline (23). Accordingly, Doppler and tissue Doppler measurements were performed using 2.5 MHz and 2.5-3.5 MHz probes, respectively. Left ventricular end-systolic and diastolic volumes were measured in the apical two-chamber and four-chamber views. The ejection

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fraction (LVEF) was calculated according to the Simpson method Fig(1) shows the Simpson method for evaluation of the left systolic function. The right ventricular diameter at the end of the diastole and in the middle of the right ventricle was measured in the apical four-chamber view. In order to standardize the volumetric comparisons, atrial and ventricular volumes were indexed according to the body surface area (BSA).

Right ventricular fractional area change (RVFAC) is one of the right ventricular systolic function parameters and was calculated as follows:

RVFAC= (End diastolic area of the RV – End systolic area of the RV) / End diastolic area of RV

Tricuspid Annular Plane Systolic Excursion (TAPSE), which means the amount of longitudinal movement of the tricuspid annulus towards the apex in the systole, is another parameter of systolic function. It was measured by M-Mode echocardiography in an apical four-chamber view by aligning the probe with the lateral annulus which was determined by measuring the distance of annular excursion along a longitudinal line in the systole (24). Fig (2) shows Tricuspid Annular plane systolic Excursion(TAPSE)

To determine the right ventricular diastolic function, the earliest peak (E) and the latest peak (A) of diastolic flow velocity, along with their E/A ratio, and the deceleration time (DT) were recorded which are placed in a parallel position with the RV inflow in an apical four-chamber view and then the sample size would be positioned at the tip of the tricuspid valve leaflets. Evaluations were done at the end of the exhalation and as a final result, the last 3 exhalation cycles will be averaged out. Fig(3) shows the trans-tricuspid flow and delineated with pulse wave Doppler presenting E and A waves

Tissue Doppler echocardiography

Tricuspid annulus lateral velocities are measured in an apical 4-chamber

view using pulse-wave tissue Doppler echocardiography only when there is maximum parallelism with the RV wall. Colorful TDI is used in addition to 2D images with depth and angle adjustment to achieve adequate frame rates. The sample size (2-4 mm) would be placed at the junction between the tricuspid valve lateral leaflet and the RV wall. Furthermore, the measurements are carried out at the end of the exhalation and the decision criterion would be the average of 3 cycles. One positive systolic wave (s'), a premature negative diastolic wave (e') and a late negative diastolic wave (a') will be formed which then will be used to calculate the velocities of s',e', and a' waves. The velocity scale will be set to SS 20 (m/s) and the recording speed is 100-50 mm/s. Fig(4) displays right ventricular tissue using pulse wave tissue Doppler in apical 4-chamber view.

Statistical analysis

Statistical analysis was performed using SPSS software version 23. The qualitative variables were reported as frequency and percentage while the quantitative ones were reported as mean and standard deviation. Qualitative data of the groups were compared using the chi-square test and, if necessary, Fisher's exact test. On the other hand, the quantitative data were compared using an independent t-test. A P-value of less than 0.05 was considered statistically significant.

Results

The mean patient age in both groups was 54+-10 years. There was no significant difference in baseline variables including gender, weight, medications, history of diabetes, and hypertension ($p>0.05$).

According to Table 1, the groups showed no significant difference in left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume index (LVEDVi) and left ventricular end-systolic volume index (LVESVi) ($P>0.05$). No significant difference in any of the parameters of right ventricular systolic and diastolic function was found ($P>0.05$). Right and left ventricular function parameters were in the normal range in the majority of patients in both groups and there was no association between Vit-D deficiency and ventricular dysfunction.

Table 1. Left Ventricular systolic function parameters based on the Vit-D level

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P-value	Patients with Vit-D deficiency	Patients with normal Vit-D	criteria	Parameter*	Parameter*
0.420	37 (78.7%)	19 (70.4%)	normal	LVEF	LV
	10 (21.3%)	8 (29.6%)	abnormal		
0.100	46 (97.9%)	24 (88.9%)	normal	LVEDVi	
	1 (2.1%)	3 (11.1%)	abnormal		
0.340	42 (89.4%)	22 (81.5%)	normal	LVESVi	
	5 (10.6%)	5 (18.5%)	abnormal		

* LV: left ventricular; EF: ejection fraction; LVEDVi: LV end-diastolic volume index; LVESVi: LV end-systolic volume index;

Table 2. Left Ventricular systolic function parameters based on the Vit-D level

0.277	45 (95.7%)	27 (100%)	[?]34	RAVi (ml/m^2)	RV
	2 (4.3%)	0 (0.0)	>34		
0.184	47 (100%)	26 (96.3%)	>120	DT)ms(	
	0 (0.0)	1 (3.7%)	>120		
0.623	36 (76.6%)	22 (81.5%)	>35	FAC (%)	
	11 (23.4%)	5 (18.5%)	<35		
0.749	35 (74.5%)	21 (77.8%)	>10	RVSM (cm/ms)	
	12 (25.5%)	6 (22.2%)	<10		
0.623	36 (76.6%)	22 (81.5%)	[?]1.6	TAPSE (cm)	
	11 (23.4%)	5 (18.5%)	<1.6		

* RV: right ventricular;; DT: deceleration time; EF: ejection fraction; FAC: fractional area change; RAVi: right atrial volume index; RVSM: right ventricular peak systolic myocardial velocity; TAPSE: tricuspid annular plane systolic excursion

Table 3. Right Ventricular diastolic function parameters based on the Vit-D level

P-value	Patients with Vit-D deficiency	Patients with normal Vit-D	criteria	Parameter*	Parameter*
0.646	21 (44.7%)	15 (55.6%)	No diastolic dysfunction	E/A	RV
	12 (25.5%)	5 (18.5%)	Impaired-relaxation		
	14 (29.8%)	7 (25.9%)	Pseudo-normal		
	0 (0.0)	0 (0.0%)	Restricted relaxation		
0.914	18 (38.3%)	10 (37%)	>6	E/E´	
	29 (61.7%)	17 (63%)	<6		

A: peak velocity of late diastolic transtricuspid flow; E: Peak velocity of early diastolic transtricuspid flow; E': peak velocity of early diastolic tricuspid annular motion;

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Discussion

Ventricular function parameters can be measured accurately via invasive methods, but due to the impossibility of performing them in everyday medicine, alternative methods are required. According to current guidelines, echocardiographic parameters are used to evaluate ventricular systolic and diastolic function (25). The results of this study showed that, in general, there is no significant difference between the groups in ventricular function determined by echocardiographic parameters. In other words, there was no significant relationship between ventricular systolic function and Vit-D status.

Different or even contradictory results are found for the relationship between vitamin D levels and left and right ventricular function. In our study, no difference was observed between the groups regarding left ventricular systolic function. Similarly, Macedo et al. (26) studied 640 individuals of the general population and found no significant difference in LVEF and wall velocity (S) based on the Vit-D status. Similar results were also observed in a retrospective study by Pandit et al. (27) on 1011 patients. However, Jorge et al. (28) studied patients with suspected heart failure but normal EF, and reported that although there was no difference in LVEF, the wall velocity (S) was significantly lower in the Vit-D deficient group, indicating systolic dysfunction. Similar to the results of the current study, Pandit et al. (27) found no Vit-D status dependence of left ventricular diastolic function parameters including diastolic E/E', E/A(Table 3), and left ventricular muscle mass index (LVMi), left atrial volume index (LAVi), and mitral valve DT. Macedo et al.(Table 1) (26) did not find a significant difference in the left ventricular end-diastolic diameter and volume (LVEDD and LVEDV), however, they reported that left atrial diameter and volume (LAD and LAV) were significantly higher in Vit-D deficient group (3.42 cm vs. 3.3 cm and 38.73 ml vs. 35.8 ml, respectively)(Table 1). They concluded that this difference may be related to Vit-D deficiency, but these differences were small and the values should be corrected based on body surface area (BSA) before comparison. They showed that LADi was not statistically significant for both groups, and although the difference in LAVi was still significant, it was very small and was in the normal range in both groups based on echocardiography guidelines (23). In the study performed by Jorge et al. (28) on the Vit-D deficient group, the E/E' ratio was significantly higher (15.5 vs. 7.5) but E' was significantly lower (7.6 vs. 9.4), indicating more severe left ventricular diastolic dysfunction in Vit-D deficient group. In a study conducted by Akin et al. (29), diastolic function parameters (including LAD, isovolumic relaxation time (IVRT), and E/E' ratio) were significantly higher in the Vit-D deficient group, but the differences were also 0insignificant. Rahman et al. (30) reported completely different results in their study. They evaluated 60 patients with systolic heart failure and found that although the left ventricular systolic function was worse in Vit-D deficient group, diastolic function was reported better. Thus, an ambivalent role was proposed for Vit-D in systolic and diastolic function.

Overall, there are conflicting results reported by different researchers, indicating that there must be other variables in addition to the difference in the study population.

Conclusion

The results of this study showed that, in general, there is no significant difference between the groups in ventricular function determined by echocardiographic parameters. In other words, there was no significant relationship between Left and Right ventricular systolic/and Right ventricular diastolic function as a precursor state of the RV systolic dysfunction, and Vit-D status (Table 1,2,3). Although some studies have shown a relationship between Vit-D levels and Left and Right ventricular systolic function, the reported differences between functional parameters were not clinically and pathophysiologically logical.

Future research suggestions

There are few studies evaluating the correlation between ventricular function and Vit-D status, and the results of available studies are also conflicting, suggesting that there may be confounding factors or population heterogeneities which make it difficult to draw conclusions. Therefore, it is recommended to conduct high-quality studies with larger sample sizes and better control of variables in order to provide conclusions with strong scientific support.

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Statements and Declarations

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Competing Interests

The authors declare no competing interests.

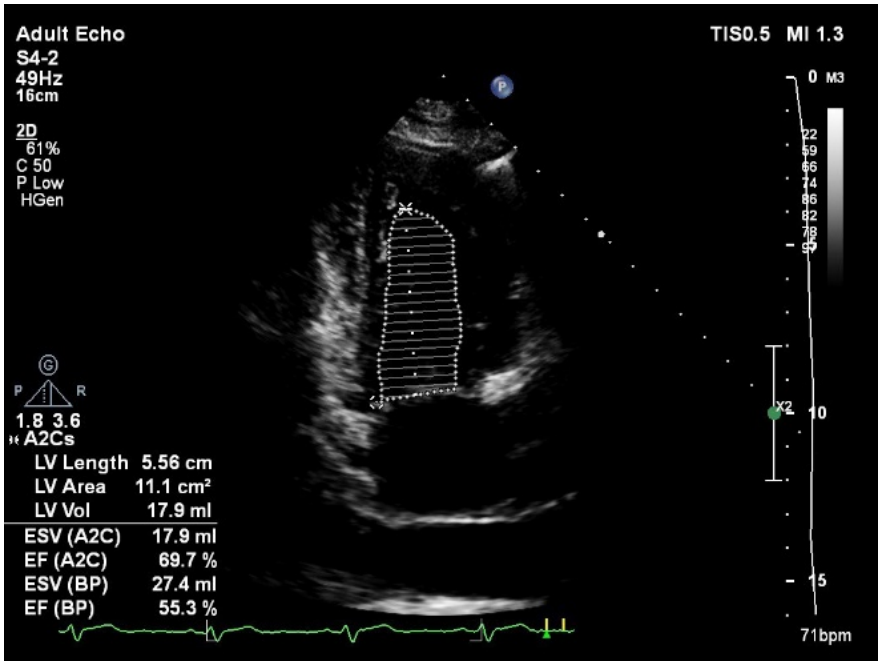

Figure 1. Simpson method for evaluation of left ventricular systolic function

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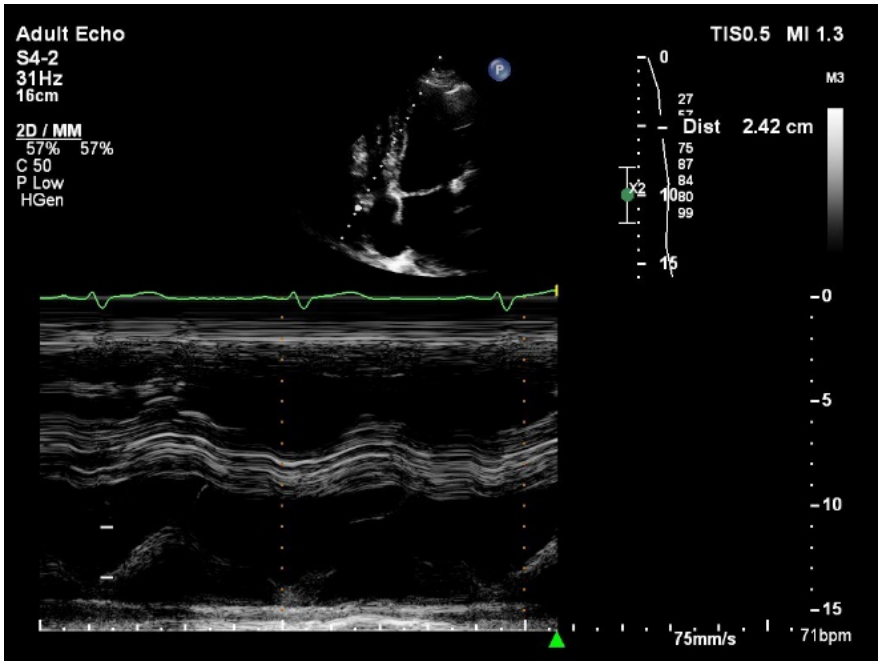

Figure 2. TAPSE (tricuspid annular plane systolic excursion) for evaluation of right ventricular systolic function

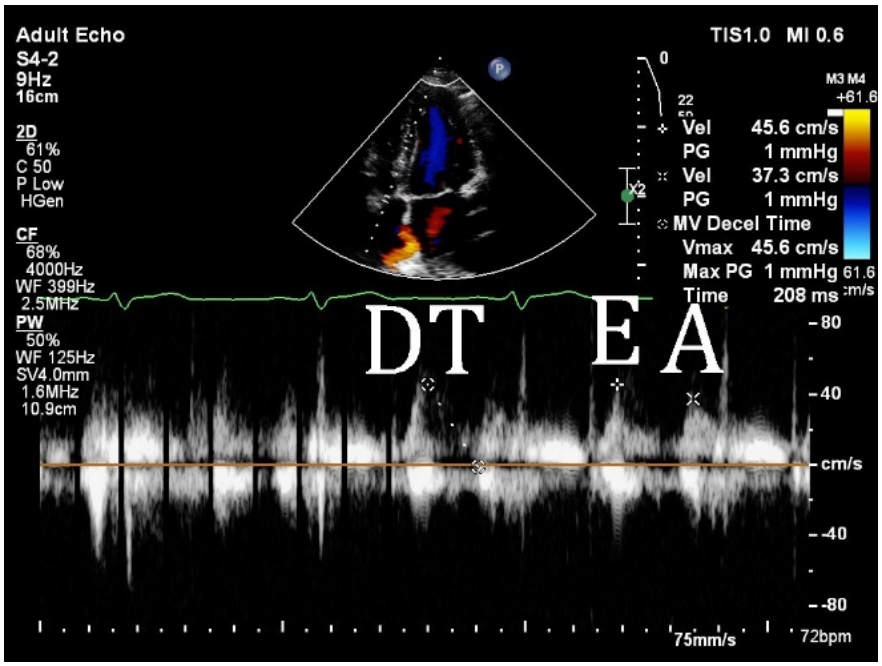

Figure 3. Tricuspid flow delineated with pulse wave Doppler presenting E and A wave and DT for evaluation of diastolic RV function

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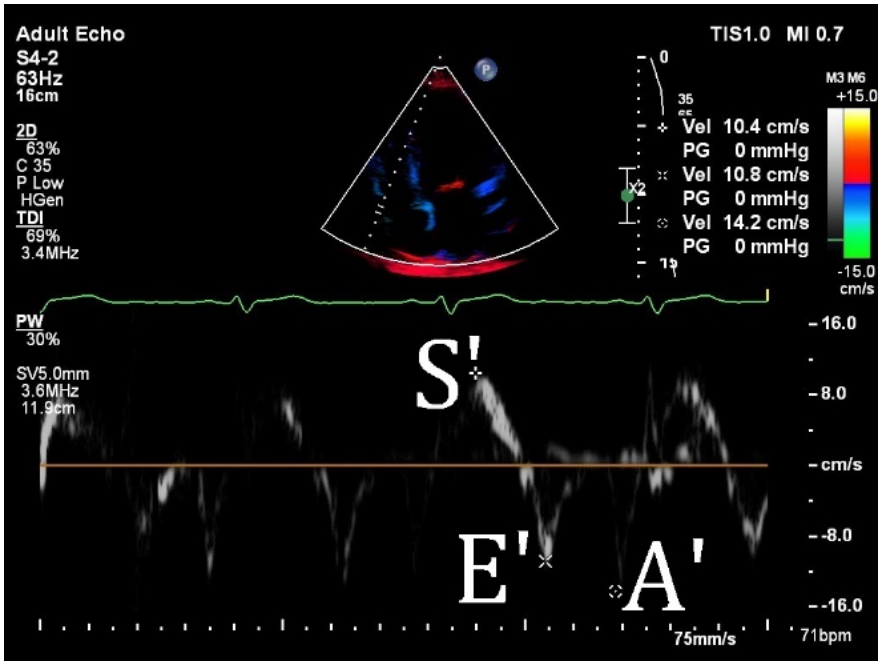

Figure 4. Right ventricular tissue delineated with pulse wave Doppler presenting S and E and A wave for evaluation of systolic and diastolic RV function

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