EFFECT OF PULMONARY HYPERTENSION SECONDARY TO CONGENITAL HEART DISEASE ON RIGHT VENTRICULAR VOLUMES AND FUNCTION: A COMPARATIVE STUDY BETWEEN TWO DIMENSIONAL, THREE DIMENSIONAL ECHOCARDIOGRAMS AND INVASIVE RV QUANTIFICATION

Yasmin A. Esmail, Ghada S. EL Shahid, Alaa M. Roushdy and Mohamed R. Hussein.

Department of Cardiology Faculty of Medicine – Ain Shams University

Corresponding author:

Mohamed R. Hussein.

Mobile: 01002086538
E mail:
Mohamed_rashad_1988@hotmail.com
Received: 11/4/2019
Accepted: 24/4/2019

ABSTRACT

Background: Quantitative echo cardiographic assessment of right ventricular (RV) function is becoming of increasing interest in cardiac diseases that affect the right ventricle, such as congenital heart disease and acute or chronic pulmonary hypertension (PH),but is still challenging due to RV complex anatomy and structure.

Aim of the Work: To study the effect of PH on the RV volumes and function using 2DE, 3DE and RV quantification by angiography in patients with PH secondary to congenital heart disease and to compare between 3D RV quantification by echocardiogram and invasive by angiography in patients with PH secondary to congenital heart disease.

Patients and Methods: This cross sectional study included all patients with congenital heart diseases complicated by pulmonary hypertension referred to cardiology department in Ain shams university hospital for elective hemodynamic assessment.

Results: The diagnostic accuracy of 3D RV and angiography (Ang.) RV parameters for detecting hemodynamic signs of pulmonary hypertension (a composite of PVR > 7) was shown by receiver-operating characteristic curves. The parameters with the largest areas under the curve (AUC) were: 3D tenting volume (1.000) had the highest area under the curve followed by mean PAP and PASP, followed by 3D-TV annulus area, Ang. RV EF,3D RV EF And lastly FAC. The best cut-off values of: 3D TV tenting volume >4.8 (Se: 100%, Sp: 100%), PASP >80(Se: 100%, Sp: 97.5%), mean PAP >50 (SE:100, SP: 97.5%), 3D TV annulus area >9.3 (SE: 100%, SP: 92.5), Ang. RV EF < =36% (SE=100%, SP= 80%), 3D RV EF <=42% (SE=100%, SP+77.5%)and RV FAC<=36 % (Se: 100%, Sp: 67.5%).

Conclusion: In PH patients, the quantitative assessment of global and regional RV function by 3D provided a useful hemodynamic and prognostic information. Several indices can be obtained by 3D echocardiography non-invasively, to predict the PVR in congenital heart disease with PH.

Key words: Pulmonary hypertension, congenital heart disease, right ventricle, two-dimensional, three-dimensional echocardiograms.

INTRODUCTION:

In understanding the progression of right ventricular (RV) failure in pulmonary arterial hypertension (PAH), a key knowledge is the mechanisms that underlie the transition from normal RV function to RV dysfunction and failure, and how these transitions are dependent on changes in

pulmonary vascular function as the disease progresses. Clinical studies have shown that elevated pulmonary vascular resistance correlates with mortality in PAH[1-3].

Cardiac magnetic resonance is currently the most reliable non-invasive tool for this purpose, mostly due to its unique spatial resolution and 3D imaging capacity. Cardiac magnetic resonance is, however, inapplicable in certain patients (e.g. with claustrophobia or implanted metallic devices). In addition, its wide use is precluded by cost, long scan and analysis time, limited availability, and dedicated expertise. Moreover, CMR has limited ability to assess load-independent parameters (such as myocardial contractility) in patients with long-standing pressure overloaded RV.

Accurate volume analysis independent of RV size and shape, without foreshortened views and geometric assumptions ensure the superiority of RT3DE for RV quantitation over the conventional echocardiography methods. Good correlation between RT3DE and CMR for calculating RV volumes and EF was reported. Compared with CMR data, RV volumes calculated from 3D echocardiography showed significantly better agreement and lower intra- and inter observer variability than 2D echocardiography.

Right heart catheterization is the gold standard method for diagnosis of pulmonary hypertension and an important tool for testing the eligibility of patients with CHD to undergo operations for correction of heart defects[5-13]. PVR is routinely calculated - using catheterization-derived measurements - as the ratio of the transpulmonary pressure gradient (Δ p) to flow (Qp)[3,4] The invasive nature of this measurement might increase patient's risk and therefore, tends to restrict the frequency with which it is obtained. As newer therapies for PH emerge and cardiothoracic surgeons accept patients with higher and higher PVR, a noninvasive method that would allow more frequent measurements of PVR may prove useful[2,3,4].

AIM OF THE WORK:

1. To study the effect of PH on the RV volumes and function using 2De, 3DE and RV quantification by angiography in patients with PH secondary to congenital heart disease.

2. To Compare between 3D RV quantification by echocardiogram and invasive by angiography in patients with PH secondary to congenital heart disease.

- **Type of Study:** cross sectional study
- **Study Period:** over a period from 2017-2018
- **Study Population :**

Inclusion Criteria:

The study included all patients with congenital heart diseases complicated by pulmonary hypertension referred to cardiology department in Ain shams university hospital for elective hemodynamic assessment.

- **Exclusion Criteria:**

- Subjects with other conditions that can cause pulmonary hypertension, prior surgery that required operative manipulation of the RV, cardiomyopathy, arrhythmias, comorbidities, insufficient ultrasound image quality (defined as more than 3 myocardial segments that were not optimally visualized using conventional 2DE), any contraindication to catheterization, any contraindication to general anesthesia and any complex congenital heart disease rather than simple intracardiac shunts

- **Sample Size**: all patients with congenital heart diseases complicated by pulmonary hypertension referred to

cardiology department in Ain shams university hospital for elective hemodynamic assessment over a period from 2017-2018.

- **Ethical Considerations:**

- Approval of Ain Shams University ethical committee
- Informed consent was obtained from all patients.
- All the patients in the master table were coded by numbers to preserve their confidentiality and no one has right to read the patient medical information except the main researcher.
- Study Procedures: all procedures were carried out by the most competent personal in our institution

A. Before catheterization:

❖ Two dimensional Echocardiography*:*

Transthoracic echocardiographic exami-nation using a Vivid 5, Vivid E9 or S5 machine with an M4S matrix sector array probe with a frequency of 2.5 MHZ (General Electric Vingmed Ultrasound, Horten, Norway). M-mode, two dimensional, tissue Doppler as well as pulsed and continuous Doppler flow across the different heart valves in all the standard views are to be done with particular emphasis on:

I. RV fractional area change*(RV FAC).*

II. Tricuspid annular plane systolic excursion (*TAPSE*).

III. Pulmonary artery systolic pressure *(PASP)* and mean pulmonary artery pressure

IV. Different congenital heart diseases like ventricular septal defect, Patent ductous arteriosus, Atrialseptal defect, common AV canal.

❖ Three dimensional Echocardiography:

3DE was done using a dedicated wide-angle, broadband 4V (GE E95) matrix-array transducer to allow for full cover of the entire RV by the pyramidal volume, with special attention to the outflow tract and upper anterior wall.

After offline analysis all the following data was obtained:3D EDV, 3D ESV, 3D EF,3D Stroke volume indexed ,3D Model of RV, 3D Tricuspid valve area and 3D TV tenting volume.

B. Catheterization:

❖ The pulmonary vascular resistance PVR in Wood units (WU) will be calculated.

❖ RV quantification by angiography:

For calculation of angiographic volumes, the thirty-degree right anterior oblique (RAO) view will be utilized. The diastolic and systolic images will be selected, and a contour drawn. The area within the contour will be then calculated.

Statistical Analysis:

Data are going to be presented as mean ± SD. Regression analysis are to be used to relate Doppler parameters to hemodynamics. Significance will be set at a p value ≤ 0.05.

RESULTS

Patient demographic and baseline data:

50 patients with simple congenital heart disease complicated with PH were included in the study. One patient was excluded due to in accurate measurement of 3D RV volumetric analysis (unsatisfactory echo-cardiographic window due to missing the anterior wall of the RV). The final study comprised 49 patients (Female =30 patient s, Males= 19 patients) as shown in figure (1)

Demographic characteristics of 49 patients were shown in table (1).

Table (1):

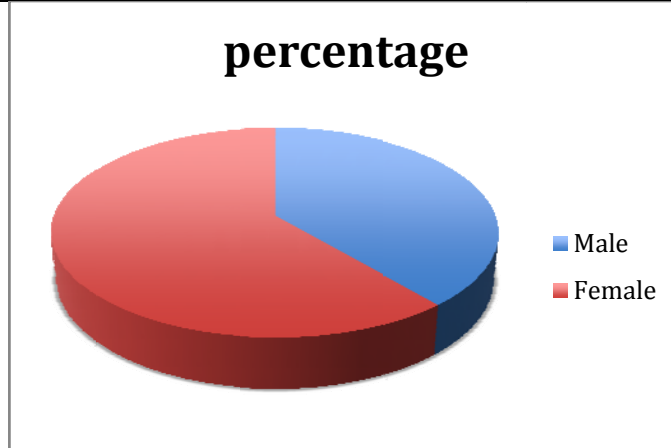|	N	Mean	SD	Minimum	Maximum
Age	49	19.224	16.1391	3.000	65.000
Height(cm)	49	132.796	32.3232	75.000	178.000
Weight(kg)	49	45.939	28.5893	5.000	95.000
BSA	49	1.227	0.5543	0.400	2.130

Figure (1): Pie chart demonstrates the percentage of both genders in the study group.

The patients were classified in to subgroups according the underlying congenital defectas shown in figure (2):ASD (n=20, 40.8%), PDA (n= 12, 24.5%), VSD (n=13, 26.5%), CAVCD (n=3, 6.1%), TAPVD(n=1, 2%)
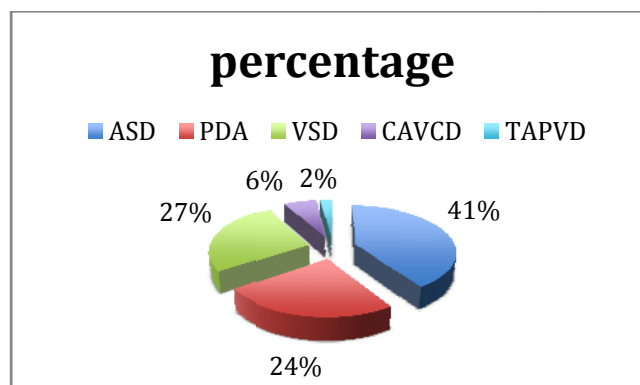

Figure (2): Piechart demonstrates the subgroups of the study population.

Considering the entire study population, real time 3D images were successfully analysed in 49 patients as shown in table (2).

Table (2):

	N	Mean	SD	Median	Minimum	Maximum
3D,RV ESV(ml/m2)	49	47.245	29.8430	41.000	17.000	194.000
3D,RVEDV (ml/m2)	49	82.449	42.7157	75.000	35.000	303.000
3D SV i	49	35.184	15.0813	33.000	15.000	109.000
3D TV area	49	6.647	3.9727	4.700	1.700	18.600
3D RVEF	49	43.216	8.1895	46.000	26.700	58.500
3D Tricuspid tenting volume	49	3.118	2.2258	2.200	0.600	9.500

Angiography RV volumes quantification were successfully analysed in 49 patientsas shown in table (3).

Table (3)

	N	Mean	SD	Minimum	Maximum
Angiography SVi	49	40.849	17.8290	15.000	90.000
Angiography RVEDV (ml/m2)	49	107.414	58.7876	35.000	334.000
PVR (woods)	49	4.758	3.0539	1.300	13.400
Angiography RVEF	49	40.198	11.0507	21.000	66.000
Angiography RVESV (ml/m2)	49	66.435	46.5777	13.000	244.000

Conventional 2D echocardiography parameters of RV   were successfully analysed in 49 patients as in table (4).

Table (4)

	N	Mean	SD	Minimum	Maximum
Mean PAP(mmhg)	49	33.633	23.8036	10.000	98.000
PASP(mmhg)	49	51.796	39.2242	13.000	156.000
RV FAC	49	36.920	10.4570	15.200	54.200
TAPSE (mm)	49	17.92	5.4766	3.000	28.000

Correlation figures:

We compared 3D RV parameters, Angiography RV parameters with PVR, we found that both of them are statistically correlated with PVR, however 3D RV EF has a stronger linear correlation with PVR than Ang. RV EF depending on r value (3D RV EF r = -0.666; p < 0.001), angiography performance (r = -0.588; p < 0.001) figures(4, 5), both of them are far better than 3D RV volumes and angiography RV volumes with PVR.

The RV EF and volumes measured by 3D echocardiography and quantified by angiography were compared with each other, a strong linear correlation were detected between:

3D RV EF and angiography RV EF (r = 0.847; p < 0.001), Figure (3).

3D RV EDV and angiography RV EDV (r = 0.817; p < 0.001),

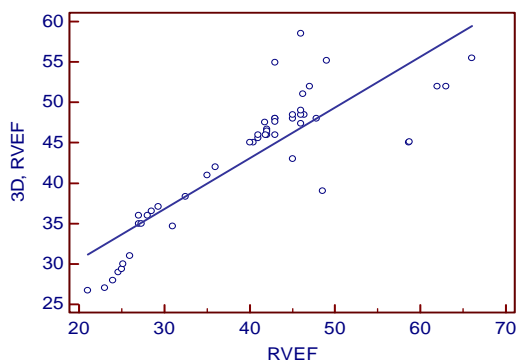The same between 3D RV ESV and Angiography RV ESV (r = 0.870; p < 0.001).

Figure (3): Significant correlation between Angiography RV EF and 3D RV EF
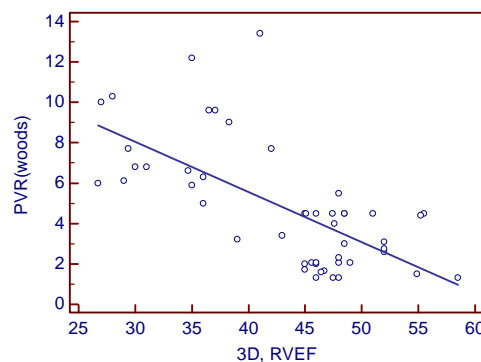

Figure (4): correlation between 3D RV EF and PVR
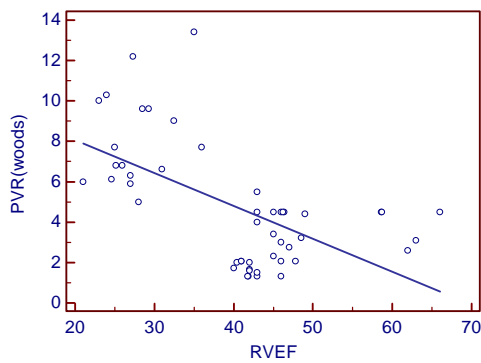
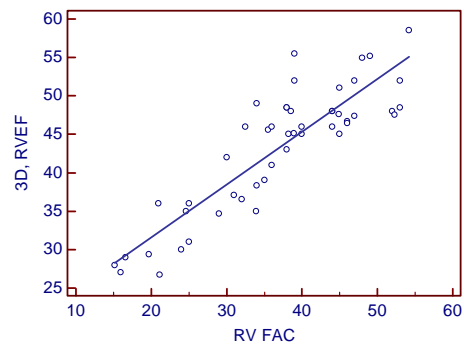Figure (5): correlation between Angiography RV EF and PVR

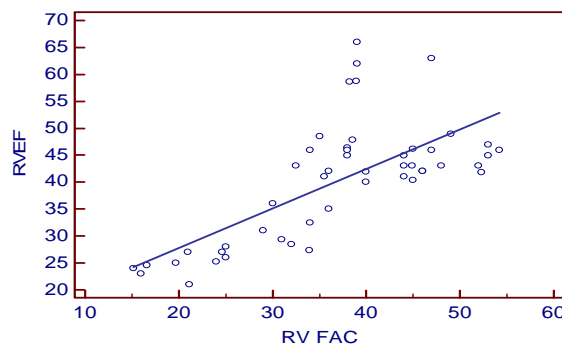Figure (6): correlation between 3D RV EF and RV FAC

Figure (7): correlation between Ang. RVEF and FAC

3D and conventional 2D echocardiography parameters were compared with each other) where 3D RV EF was strongly correlated with PASP and mean PAP in negative manner than Angiography RV EF (3D RV EF with PASP r= -0.755, 3D RV EF with PAPm, r= -0.729) (Ang. RV EF with PASP, r= -0.697, Ang. RV EF with PAPM, r = -0.681).

Convention function parameters of RV in terms of RV FAC and TAPSE were compared with 3D RV EF. We observed a strong linear positive correlation between 3D RV EF and FAC (r= 0.879) figure (6) than 3RVEF with TPASE (r= 0.577), similar correlation was found between this conventional parameter and Angiography RV EF figure (7).

PVR showed a negative significant correlation with RV FAC (r= -0.617, p<0.0001), however no correlation was detected between it and TAPSE (r=-

0.185,p= 0.2043) Analysis of 3 subgroups showed the following correlation: Figure (8)

Both PDA and VSD subgroups showed a strong negative linear correlation between 3D and Ang. RV EF with PVR (VSD 3D RV EF r= -0.708 , Ang. RV EF, r= -0.745) (PDA subgroup 3D RV EF, r=-0.717, Ang. RV EF, r= -0.722), while the ASD subgroup approached a weak negative correlation between the 3D RVEF and Ang. RV EF with PVR (ASD 3D RV EF r= -0.412 , Ang. RV EF r= -0.295) .

RV EDV and RV ESV measured by the 3D echocardiography and angiography showed strong positive correlation among the 3 subgroups (r=0.9).

Among the conventional 2D RV parameters between the 3 subgroups, the RV FAC showed strong negative correlation with PVR in the VSD and PDA subgroups only (r=-0.689, / r=-0.639 respectively).
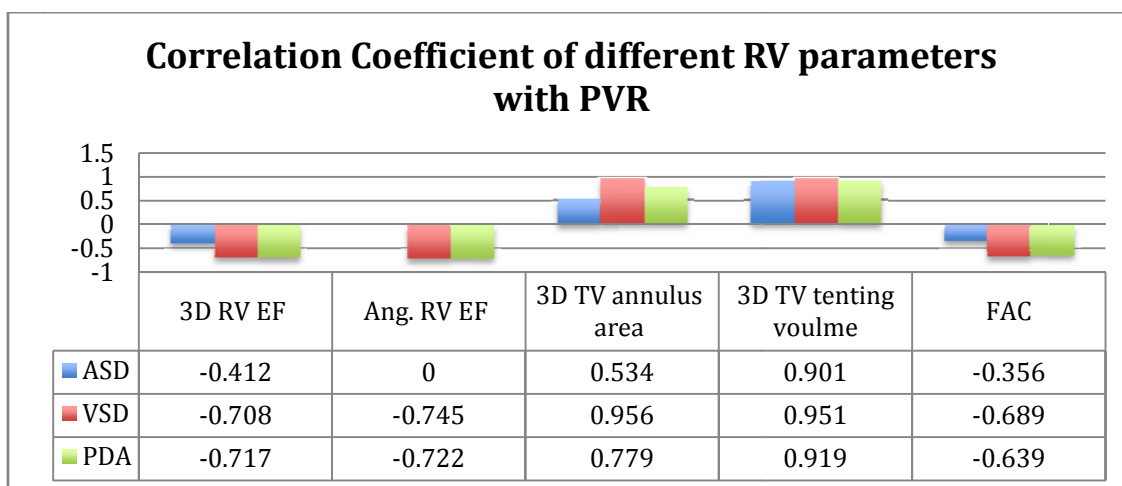
Figure (8): Correlation Coefficient of different RV parameters with PVR

DISCUSSION:

Our report differs from previous literature in some respects. First, we analysed comparatively the diagnostic accuracy of 3D RV EF and RV EF by angiography, showing a better association with hemodynamic variables reflecting pulmonary hypertension than standard echo indices. To the best of our knowledge, this is the first study assessing the relation between these echocardiographic and angiographic indices with the hemodynamic parameters indicative of pulmonary hypertension in congenital heart disease, this finding showed an additional value compared to standard echo parameters, since the current guidelines point out the importance of early diagnosis of PH and RV failure.

Despite the fact that medical therapies reduce PVR, the prognosis of patients with PAH is still poor. The primary cause of death is right ventricular (RV) failure. One possible explanation for this apparent paradox is the fact that a reduction in PVR is not automatically followed by an improvement in RV function and this can be evident by Van de Veerdonk MC, et al, 2011[14] where after PAH-targeted therapy, RV function can deteriorate despite a reduction in PVR. Loss of RV function is associated with a poor outcome, irrespective of any changes in PVR. So early prediction of RV failure will initiate early targeted treatment and improve the outcomes regardless PVR.

In Our study we detected a strong correlation between 3D RV and angiography RV parameters(EF and volumes) , This concept was proven in a different manner by Andrew N, et, al 1988 ,[15] who proved a strong correlation between the RV volume cast measured by fluid displacement and that measured by biplane angiography .

Our study has shown that there is no statistically significant correlation between the 3D and angiography RV volumes with PVR. This is due to the fact that RV volumes is not solely affected by the pressure overload in congenital intracardiac shunts with pulmonary hypertension, other factors contribute to enlargement of RV volumes for example the additional volume overload in ASD patients.

This was endorsed by, Pei-Ni Jone, et al, 2017[16] they conducted a study to evaluate right ventricular functional indices using 3D echocardiography (3DE) between normal children and paediatric pulmonary hypertension (PH) patients, and to evaluate

these indices as outcome predictors in children with PH.

The study showed that PH patients had higher RV volumes, lower RV EF and this was similar to our study, They concluded that An EDVi ≥ 102 mL/m2, ESVi ≥ 54 mL/m2, SVi ≤ 37 mL/m2, 3D. EF ≤ 43% were significantly associated with increased risk of adverse clinical events. However, in our study, we could not obtain neither a significant correlation nor cut off values for RV volumes and indexed stroke volume in relation high PVR.

Moreover, this is the first study to use the values of 3D RV EF, 3D TV annulus area , 3D TV tenting volume and angiography RV EF to predict PVR > 7 woods in patient with intracardiac shunts complicated with pulmonary hypertension .

On the other hand, Antoniviteralli, et al[17] , had conducted study in 2015   to evaluate the three-Dimensional Echocardiography and 2D-3D Speckle-Tracking Imaging in Chronic Pulmonary Hypertension due to different aetiologies and not congenital heart dieses in particular, they detected a cut off value of 3D RVEF to predict the early RV failure rather than the PVR as obtained in our study

Conclusions:

Based on the results of the current study it can be concluded that:

- In PH patients, the quantitative assessment of global and regional RV function by 3D provided us useful hemodynamic and prognostic information.

- Several indices can be obtained by 3D echocardiography non-invasively, predict the PVR in congenital heart disease with pulmonary HTN.

- This is the first study to define the Role of RV quantification by angiography

and it is strong correlation with 3D RV indices.

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Yasmin A. Esmail, et al.,

تأثير ارتفاع ضغط الدم الشرياني الرئوي بسبب أمراض القلب الخلقية على احجام البطين الأيمن والوظيفة : دراسة مقارنة بين تخطيط صدى القلب ثنائي وثلاثي الأبعاد وبين أحجام البطين الأيمن عن طريق تَصْوِيرالأَوعِيَة

الخلفية: أصبح التقييم الكمي لتخطيط صدى القلب لوظيفة البطين الأيمن (RV) ذات اهمية في أمراض القلب التي تؤثر علىالبطين الأيمن ، مثل أمراض القلب الخلقية وارتفاع ضغط الشريان الرئوي الحاد أو المزمن (PH) ، لكنه لا يزال يمثل تحديًا بسبب التكوين المركب للبطين الأيمن RV .

الهدف من العمل: دراسة تأثير ارتفاع ضغط الدم الشرياني الرئوي بسبب أمراض القلب الخلقية على أحجام البطين الأيمن والوظيفة باستخدام تخطيط صدى القلب ثنائي و ثلاثي الأبعاد و أحجام البطين الأيمن عن طريق تَصْوِير الأَوعِيَة في المرضى المصابين بارتفاع ضغط الشريان الرئوي المزمن نتيجة أمراض القلب الخلقية والمقارنة بين أحجام البطين الأيمن عن طريق صدى القلب وعن طريق تَصْوِير الأَوعِيَة في المرضى المصابين بارتفاع ضغط الشريان الرئوي المزمن نتيجة أمراض القلب الخلقية.

الحالات وطرق البحث: سوف تتضمن الدراسة كل المرضى الذين يعانون من أمراض القلب الخلقية المعقدة بسبب ارتفاع ضغط الدم الرئوي المحالين لقسم أمراض القلب بمستشفى جامعة عين شمس من أجل التقييم الدِيناميكي الدَمَوي التداخلي في الفترة من٢٠١٧الي ٢٠١٨ .

. النتائج: تم إظهار الدقة التشخيصية لثلاثي الأبعاد والتصوير الوعائي للبطين الايمن RV للكشف عن علامات الدورة الدموية لفرط ضغط الشريان الرئوي (مركب من PVR< ٧) بواسطة منحنيات مميزة تعمل للمستقبل. كانت المعلمات التي تحتوي على أكبر المساحات تحت المنحنى (AUC) هي: يحتوي حجم الخيمة ثلاثية الأبعاد للصمام ثلاثي الشرفات (١.٠٠٠) على أعلى مساحة أسفل المنحنى متبوعًا بالترتيب تدفق القَلَس الرئوي PASP و متوسط ضغط الشريان الرئوي ، متبوعًا بمساحة الحلقة ثلاثية الأبعاد للصمام ثلاثي الشرفات ،الكَسْر القَذْفِي للبطين الأيمن Ang. RV EF الكَسْر القَذْفِي للبطين الأيمن ثلاثي الابعاد D RV EF٣ ، وأخيرا المنطقة الكسرية بالبطين الأيمن FAC. أفضل قيم القطع: حجم الخيمة ثلاثية الأبعاد للصمام ثلاثي الشرفات < ٤.٨ (Se: ١٠٠ ٪ ، Sp: ١٠٠ ٪) ، تدفق القَلَس الرئوي <٨٠(Se:١٠٠%, Sp٪٩٧.٥%), متوسط ضغط الشريان الرئوي> ٥٠(SE:١٠٠, SP: ٩٧.٥%) , مساحة الحلقة ثلاثية الأبعاد للصمام ثلاثي الشرفات<٩.٣ (SE: ١٠٠% SP, ٩٢.٥ %), الكَسْر القَذْفِي للبطين الأيمن بالتصوير الوعائي > ٣٦% (SE=١٠٠%, SP= ٨٠ %)، الكَسْر القَذْفِي للبطين الأيمن ثلاثي الابعاد =>٤٢% (SE=١٠٠%, SP+٧٧.٥%)، واخيرا المنطقة الكسرية بالبطين الأيمن =>٣٦ % (Se: ١٠٠%, Sp: ٦٧.٥%).

الخلاصة: في مرضى ارتفاع ضغط الشريان الرئوي المصاحب للعيوب الخلقية PH ، قدم لنا التقييم الكمي لوظيفة البطين الأيمن الكُلّي والجزئي بواسطة تقنية ثلاثية الابعاد والتصوير الوعائي للبطين الأيمن معلومات مفيدة للديناميكية الشريان الرئوي.كما يمكن الحصول على العديد من المؤشرات عن طريق تخطيط صدى القلب ثلاثي الأبعاد بشكل غير جراحي ، وتنبؤ لفرط ضغط الشريان الرئوي PVR في أمراض القلب الخلقية مع ارتفاع ضغط الشريان الرئوي.