Diagnostic tools in the follow-up and monitoring of congenital heart disease and pulmonary hypertension

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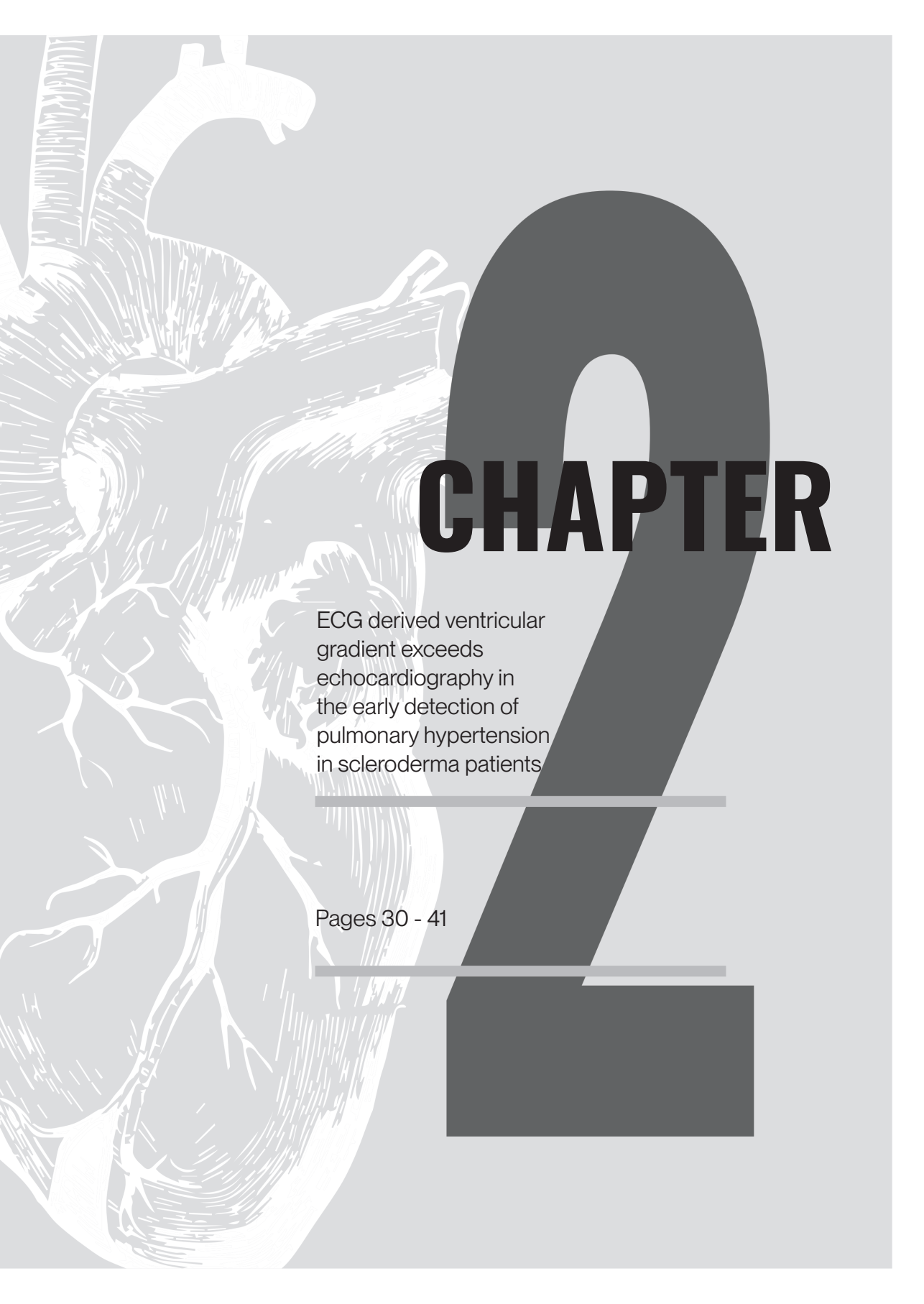
CHAPTER 2

ECG derived ventricular
gradient exceeds
echocardiography in
the early detection of
pulmonary hypertension
in scleroderma patients

Pages 30 - 41

ECG DERIVED VENTRICULAR GRADIENT EXCEEDS ECHOCARDIOGRAPHY IN THE EARLY DETECTION OF PULMONARY HYPERTENSION IN SCLERODERMA PATIENTS

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ABSTRACT

Background

Patients with systemic sclerosis (SSc) are at risk for developing pulmonary hypertension (PH) which is a major cause of death in this population. Echocardiographic (TTE) derived pulmonary arterial pressure (PAP) can be unreliable for the early detection of PH. Previous studies demonstrate that the ECG derived ventricular gradient optimized for right ventricular pressure overload (VG-RVPO) can detect PH in a heterogeneous population suspected of PH.

The aim of this study is to assess the use of the VG-RVPO as a screening and monitoring instrument of early PH in SSc patients.

Methods

Serial ECGs and TTEs from twenty-seven SSc patients who underwent right heart catheterization (RHC) were retrospectively analyzed. The changes in PAP and VG-RVPO over time were studied in patients with and without diagnosed PH.

Results

Twenty-four patients (52.5% female, mean age 58.4 years SD 14.3) were studied. In eleven patients PH was confirmed with RHC. In these patients VG-RVPO was significantly higher -8 ± 19 than in patients without PH -23 ± 10 mV· ms, (P<0.05). In addition, in PH patients the VG-RVPO increased over time in contrast to patients without PH (P<0.01). The VG was more sensitive to detect disease progression in earlier stages of disease as compared to

echocardiographic derived PAP.

Conclusions
The VG-RVPO is a sensitive, non-invasive and cost effective tool for early detection of PH in SSc patients. Serial measurements indicate that the VG-RVPO can be used as a follow-up instrument and outperforms TTE to detect early changes in right ventricular pressure over time.

Introduction
Patients with systemic sclerosis (SSc) have a high risk on developing pulmonary arterial hypertension (PAH) which is a major cause of death in this patient group. The high mortality rates can be partly explained by disease-related comorbidities but also by a relatively late diagnosis in routine clinical practice [1]. Recent cohorts studies show that PH develops in 5-15% of the patients and that early intervention with PAH-targeted therapy is beneficial in patients who are mildly symptomatic [2, 3]. Current practice in screening for pulmonary hypertension (PH) in this high risk group mainly relies on symptoms and abnormal findings on transthoracic echocardiography (TTE). In a multicenter study aiming at the development of a screening algorithm in SSc patients (DETECT study), TTE at rest using a sPAP cutoff value of 50 mmHg and dyspnea as a prominent symptom of PH were not sensitive enough to detect early forms of SSc PH [4, 5]. This underlines the need for better screening tools. Progressive PH-related pressure overload of the right ventricle (RV) causes by definition an increase in RV wall tension, and often, but not always, it causes RV hypertrophy and RV dilatation over time [6]. Previous studies show that ECG variables in advanced PH reflect physiologic and anatomic abnormalities in the right ventricle [7]. Thus the ECG may be an important non-invasive, low-cost and easy-to-obtain alternative or extra addition to the other screenings methods. However, the standard 12-lead ECG has only limited value to detect early PAH when conventionally interpreted. Other research demonstrates that the ECG derived ventricular gradient (VG), when projected on the optimal direction for detection of RV pressure overload (VG-RVPO), can detect PH in a heterogeneous population suspected of PH and in patient with SSc [8-10]. It is still unknown whether VG-RVPO can be used as a screening instrument for early PH detection, prediction of future PH, and for monitoring its course over time. In this retrospective study the aim is to assess the value of the ECG-derived VG-RVPO as a follow-up instrument in SSc patients.

Methods
The study population consisted of patients with clinically confirmed SSc who underwent

right heart catheterization (RHC) between February 2009 and February 2017. Patients took (and still take) part in a care track protocol specialized for SSc and were annually evaluated in the outpatient clinic by a rheumatologist, a cardiologist and a pulmonologist [11]. This includes a standard 10-second 12-lead resting ECG, cardio-pulmonary imaging and function tests and clinical evaluation. Patients were included in the study if they had at least 2 consecutive ECGs of good quality and corresponding echocardiograms before and after the RHC. Patients who had prior myocardial infarction were excluded. Annual performance of echocardiography and ECG is part of the care track and performed in all patients. All clinical data were prospectively collected. For the current evaluation selected patients were stratified in 2 groups: patients with and patients without RHC-confirmed PH. Included patients provided written informed consent for use of anonymous clinical data as part of the Biobank Systemic Sclerosis of the department Rheumatology of the LUMC which is approved by the Leiden University Medical Center Institutional Review Board.

ECG measurements

Standard 10-second 12-lead ECGs were recorded in the supine position. The dedicated software program LEADS (online service: www.leadsecg.com) [12] was used to measure all ECG variables used in this study. LEADS determines conventional ECG variables but also vectorcardiographic ECG variables, after mathematically synthesizing a vectorcardiogram (VCG) from the ECG. One important VCG variable is the ventricular gradient (VG). The VG is defined as the 3D integral of the heart vector over the QT interval. The VG thus gives an indication of the action potential morphology distribution in the heart [9], that changes, due to mechanic-electrical feedback, with changes in right-ventricular afterload [10, 13]. Previous research has shown that VG can detect right ventricular pressure overload (and, hence, PH) optimally by taking its projection in the 155° azimuth and 27° elevation direction [10, 14]. In the following, this optimized projection of VG is referred to as VG-RVPO (ventricular gradient – right ventricular pressure overload). Within the VCG coordinate system as it has been standardized by the American Heart Association the projection direction of VG-RVPO points to the right, slightly backward, and slightly downward. In normal hearts, VG-RVPO is usually negative, because VG points more in a leftward direction [15]. With increasing right ventricular pressure, the VG turns more rightward, and VG-RVPO becomes less negative, and, for higher degrees of RV pressure overload, even positive. In addition to VG-RVPO, other parameters including heart rate, QTc duration, QRS duration and the heart axis (QRS axis) in the frontal plane were also used in this study.

Echocardiograms

Images were obtained in the left-lateral decubitus position with a commercially available

system (Vivid 7 or E9; General Electric-Vingmed Ultrasound), using a 3.5-MHz transducer, and digitally stored in cine-loop format; offline analysis was performed using EchoPAC version BT 13 (General Electric-Vingmed). Systolic pulmonary pressure (sPAP) was calculated by summation of tricuspid regurgitant gradient (TR) and atrial pressure [16]. sPAP ≥ 34 mmHg was suspected of having PH. Right atrial pressure was estimated based on the diameter and inspiratory collapse of the inferior vena caval vein IVC [16]. The tricuspid regurgitant jet gradient (TR gradient) was calculated using the modified Bernoulli equation on the 4-chamber view [17].

Included patients had two different primary indications for RHC: risk stratification for hematopoietic stem cell transplantation (HSCT) and screening for pulmonary arterial hypertension, respectively. Patients are excluded for stem cell transplantation if they have pulmonary hypertension. Both groups were discussed in a multidisciplinary team evaluating symptoms and diagnostic test results. Indications for and interpretation of the RHC were done according to the guidelines [18]. Pulmonary arterial hypertension (PAH) (WHO group I) was diagnosed when there was an invasively measured mean pulmonary pressure (mPAP) of 25mmHg, a pulmonary arterial wedge pressure of less than15 mmHg and a pulmonary vascular resistance of more than 3 woods units [18].

Statistical Analysis

All data was analyzed using SPSS version 23 (SPSS, Chicago, IL). Continuous variables are presented as mean ± SD. Categorical variables are reported as numbers and percentages. To compare continuous variables the unpaired Student t-test and Mann-Whitney U-test were used for respectively normally or non-normally distributed variables. A total of 24 subjects, obtained as 12 in group one and 12 in group two, were each measured at 11 time points. The study achieves 90% power to detect a difference between the (fixed) group means at the last time of 9.00. The standard deviation is 12.00. The correlation between measurements within a subject is 0.500. A test based on a mixed-model analysis is anticipated at a significance level of 0.150.

Linear mixed models analysis was used to assess the differences in change in VG-RVPO and sPAP over time between the two groups [19]. The time points at which ECGs and echocardiograms were made, and at which PH was diagnosed were incorporated in the model as fixed variables. An unstructured covariance matrix was applied. A P-value <0.05 was considered statistically significant.

Results

A total of 24 patients (mean age 58±14 years, 62.5% female) were evaluated. PH on RHC was present in 11(45.8%) patients. All patients with the diagnosis PH were classified in

WHO group 1 (pulmonary arterial hypertension). The clinical characteristics of the study population at the time of RHC, are displayed in **Table 1**. The distribution of SSc subtypes in patients with pulmonary hypertension is the same. Among the 24 patients, 12 patients were also known with interstitial lung disease. Patients with PH on RHC had a significantly higher TR gradient and estimated sPAP on echocardiography. Heart rate, QRS duration, QTc duration and the percentage of patients with a right heart axis were not significantly different between the groups. VG-RVPO was significantly higher, less negative or even positive in the PH group.

Table 1. Clinical Characteristics of the study population at the time instant of RHC
**VG-RVPO and sPAP over 10 years in pulmonary hypertension versus no pulmonary hypertension**

Variable	No Pulmonary Hypertension (N=13)	Pulmonary Hypertension (N=11)	P
Age (years)	55.50 ± 16.39	61.88 ± 11.20	0.29
Females (%)	8 (61.5)	7 (63.6)	0.92
Diffuse SSc (%)	9 (69.2)	6 (54.5)	0.48
Limited SSc (%)	4 (30.8)	5 (45.5)	0.48
ILD present (%)	5 (38.8)	7 (63.6)	0.23
Echocardiography			
TR Gradient (mmHg)	25.92 ± 7.68	45.45 ± 18.12	**<0.01**
Estimated sPAP (mmHg)	32.31 ± 7.76	49.36 ± 17.37	**0.01**
LV Dysfunction present (%)	0 (0)	1 (9.1)	0.34
ECG			
Heart rate (bpm)	76.11 ± 16.55	81.48 ± 15.08	0.42
QRS duration (ms)	99.85 ± 19.33	100.73 ± 29.03	0.93
QTc duration (ms)	511.10 ± 60.25	477.50 ± 75.14	0.25
Right heart axis (º)	11.66 ± 72.164	21.9 ± 61.3	0.71
VG-RVPO (mV· ms)	-23.02 ± 10.78	-7.94 ± 18.72	**0.02**
RHC			
mPAP (mmHg)	16.85 ± 2.94	28.90 ± 4.70	**<0.01**

TR, maximum tricuspid regurgitant jet; sPAP, systolic pulmonary arterial pressure; VG-RVPO, ventricular gradient – right ventricular pressure overload. RHC, right heart catheterization. ILD; interstitial lung disease; LV dysfunction: Left ventricular ejection fraction < 40%. Data are described as numbers with frequency or mean with SD.

Figure 1 shows the VG-RVPO and sPAP over 10 years' time. The echocardiographic sPAP over time is depicted in the upper panel of fig. 1. In the initial phases of the disease (before

the RHC) the sPAP on echo of both groups did not differ significantly (95% CI -17.6 to 0, *P* = 0.43]. Also after the RHC no significant difference between the PH group and the no PH group were found. The lower panel of the figure contains the VG-RVPO, a more positive VG is associated with higher pulmonary pressures. Overall, the VG-RVPO was significantly higher in patients with PH compared to patients without PH (mean difference -17.3 Mv· ms (95% CI -25.6 to -9.1 Mv· ms, *P*<0.001). Looking closely to the first five years of the disease, that is the years before the RHC, it is noticeable that there is already a significantly higher VG-RVPO in the patients with PH compared to the patients without PH (mean difference -15.0 95% CI -24.0 to -6.2, *P*=0.002).

Figure. 1. sPAP & VG-RVPO over 10 year time
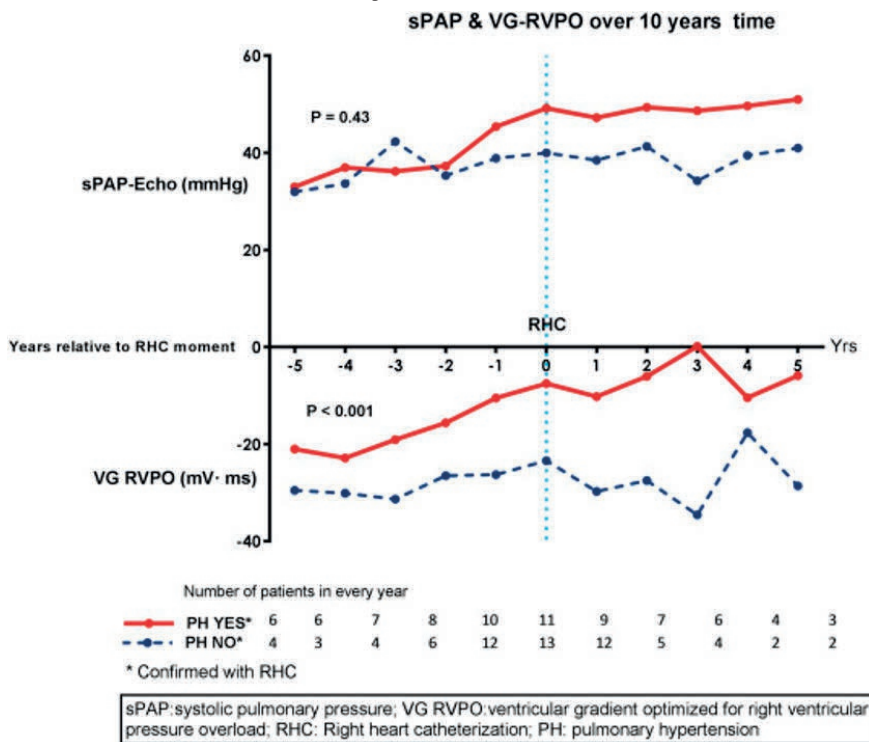
Discussion

The main finding in this study is that in patients with systemic sclerosis the vector ECG derived ventricular gradient optimized for right ventricular pressure overload, can play an important role in the monitoring and detection of PH especially in the early phases of the disease.

Current guidelines suggest that early detection and diagnosis of RV dysfunction may help to identify patients with systemic sclerosis who have subclinical PH and might benefit from early treatment [20-23]. Doppler echocardiography is a widely recognized and available tool for monitoring and screening for pulmonary hypertension in various patient groups [24, 25]. However the experience of the echocardiographer is crucial and assessment of the RV is complicated [26, 27]. The tricuspid gradient may be underestimated if the signal is weak or the regurgitant jet is not fully aligned. This is often the case in early and mild pulmonary hypertension and therefore can be an explanation for the lack of detecting elevated pressures by TTE in our study.

The standard 12 lead electrocardiogram is the most common used non-invasive diagnostic measurement in cardiology. It provides information about frequency, rhythm and conduction disorders. In addition, hypertrophy and fibrosis of both the atria and ventricles can be noticed by changes in depolarization and repolarization. The disadvantage of the standard 12 lead ECG is that it has only a limited value in the early detection of right ventricular overload [28]. One of the reasons is that the conventional ECG criteria are based on detection of right ventricular hypertrophy and this is a late phenomenon of increased pressure overload [29]. In addition, changes in the right ventricle are overshadowed by the much larger left ventricle. Therefore the routine 12-lead ECG is useful for diagnosing left ventricular pathology. A sufficient degree of right ventricular hypertrophy is necessary before the conventional ECG (and QRS) criteria are met, whereas in the early stages of PH the right ventricular wall tension is increased while hypertrophy has not developed yet [30, 31]. There are more ECG-variables to detect increased right ventricular pressure [8, 31, 14, 32-34]. These variables can easily be calculated from a digitally stored 12-lead ECG after transforming them into a VCG. The VCG analysis programs, like our LEADS program, that is available as an online service, can calculate the VG as used in our study. Actually, the VG is a measurement that includes the entire QRST complex. When right-ventricular pressure increases, there is an immediate T-wave change that reflects right-ventricular strain, and this change becomes evident in the ventricular gradient. Previous research has shown that the magnitude and direction of this ventricular gradient when projected in the optimal direction to detect RV overload is a specific marker for the presence and the severity of right ventricular overload. Couperus et al. already stated that also in patients with systemic sclerosis the ventricular gradient optimized for right ventricular pressure overload is significantly elevated when they have pulmonary hypertension [14]. The current study confirms this once more and also makes a distinction in the early phase of the disease between patients who develop PH and who not.

All patients in this study were classified in WHO group 1 (pulmonary arterial hypertension), however pulmonary fibrosis is also a leading cause of death in SSc patients [35, 36]. In our cohort 12 patient presented with interstitial lung disease. There is little literature available on ECG changes in interstitial lung disease. The right side of the heart attempts to deal with the progressive loss of vascular bed, as a result it hypertrophies [37]. Impaired gas exchange in ILD leads to important desaturation and vital organs such as the heart have a decreased oxygen delivery [38]. It is imaginable that those changes influence the ECG (and VG-RVPO). In future research the impact of interstitial lung disease on the electrocardiogram must be taken into account.

Conclusion

The VG-RVPO is a sensitive, non-invasive and cost effective tool for early detection of pulmonary hypertension in SSc patients. Moreover serial measurements indicate that the VG-RVPO can be used as a follow-up instrument and outperforms TTE to detect early changes in right ventricular pressure over time.

Limitations

Due to the retrospective nature of this study, not every ECG or echocardiogram was available at every timepoint. We only have data on a small number of patients; due to low prevalence of the disease and the strict requirements for performing an RHC. Despite these small numbers there still is a significant result which underlines the relevance and additional value of the VCG.

References

1.   Mathai SC, Hassoun PM. Pulmonary arterial hypertension in connective tissue diseases. Heart failure clinics. 2012;8(3):413-25.

2.   Hachulla E, Gressin V, Guillevin L, Carpentier P, Diot E, Sibilia J, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. Arthritis & Rheumatism. 2005;52(12):3792-800.

3.   Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A, et al. Mapping and predicting mortality from systemic sclerosis. Annals of the rheumatic diseases. 2017:annrheumdis-2017-211448.

4.   Mukerjee D, George DS, Knight C, Davar J, Wells A, Du Bois R, et al. Echocardiography and pulmonary function as screening tests for pulmonary arterial hypertension in systemic sclerosis. Rheumatology. 2004;43(4):461-6.

5.   Coghlan JG, Denton CP, Grünig E, Bonderman D, Distler O, Khanna D, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Annals of the rheumatic diseases. 2014;73(7):1340-9.

6.   Chemla D, Castelain V, Herve P, Lecarpentier Y, Brimioulle S. Haemodynamic evaluation of pulmonary hypertension. European Respiratory Journal. 2002;20(5):1314-31.

7.   Bossone E, Paciocco G, Iarussi D, Agretto A, Iacono A, Gillespie BW, et al. The prognostic role of the ECG in primary pulmonary hypertension. CHEST Journal. 2002;121(2):513-8.

8.   Henkens IR, Mouchaers KT, Vonk-Noordegraaf A, Boonstra A, Swenne CA, Maan AC, et al. Improved ECG detection of presence and severity of right ventricular pressure load validated with cardiac magnetic resonance imaging. American Journal of Physiology-Heart and Circulatory Physiology. 2008;294(5):H2150-H7.

9.   Draisma HH, Schalij MJ, van der Wall EE, Swenne CA. Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. Heart Rhythm. 2006;3(9):1092-9.

10.   Kamphuis VP, Haeck ML, Wagner GS, Maan AC, Maynard C, Delgado V, et al. Electrocardiographic detection of right ventricular pressure overload in patients with suspected pulmonary hypertension. Journal of electrocardiology. 2014;47(2):175-82.

11.   Meijs J, Schouffoer AA, Marsan NA, Kroft LJ, Stijnen T, Ninaber MK, et al. Therapeutic and diagnostic outcomes of a standardised, comprehensive care pathway for patients with systemic sclerosis. RMD open. 2016;2(1):e000159.

12.   Draisma H, Swenne C, Van de Vooren H, Maan A, van Huysduynen BH, Van der Wall E, et al., editors. LEADS: an interactive research oriented ECG/VCG analysis system. Computers in Cardiology, 2005; 2005: IEEE.

13.   Greve G, Chen R, Barron D, White PA, Redington AN, Penny DJ. Right ventricular distension alters monophasic action potential duration during pulmonary arterial occlusion in anaesthetised lambs: evidence for arrhythmogenic right ventricular mechanoelectrical feedback. Experimental physiology. 2001;86(5):651-7.

14.   Couperus L, Vliegen H, Henkens I, Maan A, Treskes R, de Vries J, et al. Electrocardiographic detection of pulmonary hypertension in patients with systemic sclerosis using the ventricular gradient. Journal of

electrocardiology. 2016;49(1):60-8.

15.   Kossmann CE, Brody DA, Burch GE, Hecht HH, Johnston FD, Kay C, et al. Recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography. Circulation. 1967;35(3):583-602.

16.   Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification. European journal of echocardiography. 2006;7(2):79-108.

17.   Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography. Journal of the American Society of Echocardiography. 2010;23(7):685-713.

18.   Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). European heart journal. 2015;37(1):67-119.

19.   Verbeke G. Linear mixed models for longitudinal data. Linear mixed models in practice: Springer; 1997. p. 63-153.

20.   Humbert M, Yaici A, de Groote P, Montani D, Sitbon O, Launay D, et al. Screening for pulmonary arterial hypertension in patients with systemic sclerosis: Clinical characteristics at diagnosis and long term survival. Arthritis & Rheumatism. 2011;63(11):3522-30.

21.   Humbert M, Sitbon O, Yaici A, Montani D, O'callaghan D, Jaïs X, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. European Respiratory Journal. 2010;36(3):549-55.

22.   Condliffe R, Kiely DG, Peacock AJ, Corris PA, Gibbs JSR, Vrapi F, et al. Connective tissue disease–associated pulmonary arterial hypertension in the modern treatment era. American Journal of Respiratory and Critical Care Medicine. 2009;179(2):151-7.

23.   Dimopoulos K, Inuzuka R, Goletto S, Giannakoulas G, Swan L, Wort SJ, et al. Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. Circulation. 2010;121(1):20-5.

24.   McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension. Circulation. 2009;119(16):2250-94.

25.   McGoon M, Gutterman D, Steen V, Barst R, McCrory DC, Fortin TA, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. 2004;126(1):14S-34S.

26.   Greil GF, Beerbaum P, Razavi R, Miller O. Imaging the right ventricle. Heart. 2008;94(6):803-8.

27.   Borgeson DD, Seward JB, Miller Jr FA, Oh JK, Tajik AJ. Frequency of Doppler measurable pulmonary artery pressures. Journal of the American Society of Echocardiography. 1996;9(6):832-7.

28.   Ahearn GS, Tapson VF, Rebeiz A, Greenfield JC. Electrocardiography to define clinical status in primary pulmonary hypertension and pulmonary arterial hypertension secondary to collagen vascular disease.

Chest. 2002;122(2):524-7.

29. Helm RA. Electrocardiographic cancellation: mathematical basis. American heart journal. 1960;60(2):251-65.

30. Harrigan RA, Jones K. Conditions affecting the right side of the heart.(ABC of Clinical Electrocardiography). British Medical Journal. 2002;324(7347):1201-5.

31. Henkens IR, Mouchaers KT, Vliegen HW, van der Laarse WJ, Swenne CA, Maan AC, et al. Early changes in rat hearts with developing pulmonary arterial hypertension can be detected with three-dimensional electrocardiography. American Journal of Physiology-Heart and Circulatory Physiology. 2007;293(2):H1300-H7.

32. KAWAGUCHI Y. Studies on deflection area vectors of QRS and T and ventricular gradient in right ventricular hypertrophy. Japanese circulation journal. 1985;49(4):395-405.

33. Cowdery CD, Wagner GS, Starr JW, Rogers G, Greenfield JC. New vectorcardiographic criteria for diagnosing right ventricular hypertrophy in mitral stenosis: comparison with electrocardiographic criteria. Circulation. 1980;62(5):1026-32.

34. Scherptong RW, Henkens IR, Kapel GF, Swenne CA, van Kralingen KW, Huisman MV, et al. Diagnosis and mortality prediction in pulmonary hypertension: the value of the electrocardiogram-derived ventricular gradient. Journal of electrocardiology. 2012;45(3):312-8.

35. Bodolay E, Szekanecz Z, Dévényi K, Galuska L, Csípo I, Vègh J, et al. Evaluation of interstitial lung disease in mixed connective tissue disease (MCTD). Rheumatology. 2005;44(5):656-61.

36. Prakash UB. Respiratory complications in mixed connective tissue disease. Clinics in chest medicine. 1998;19(4):733-46.

37. Crystal RG, Gadek JE, Ferrans VJ, Fulmer JD, Line BR, Hunninghake GW. Interstitial lung disease: current concepts of pathogenesis, staging and therapy. The American journal of medicine. 1981;70(3):542-68.

38. Lama VN, Martinez FJ. Resting and exercise physiology in interstitial lung diseases. Clinics in Chest Medicine. 2004;25(3):435-53.