Clinical validation of the planar radionuclide ventriculography in patients with right ventricular dysfunction

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A B S T R A C T

Objectives: Gated radionuclide ventriculography (RNV) may be used for the evaluation of the right ventricular function. However, the accuracy of the method should be clinically validated in patients suffering from diseases with specific pathology of the right ventricle (RV) and with possible left ventricular (LV) interaction.

Methods: Three groups of 15 patients each, diagnosed with arrhythmogenic right ventricular dysplasia (ARVD), pulmonary artery hypertension (PAH) or atrial septal defect (ASD) were compared to a group of normal subjects. The parameters for both ventricles were evaluated separately (ejection fractions: LVEF and RVEF, and interventricular synchronism quantified as phase standard deviation: LVPSD and RVPSD) as well as the relation or interdependence of the right to left ventricle (RV/LV volume ratio, LV/RV ejection fraction and stroke volume ratios, and interventricular synchronism).

All the variables as a whole were analyzed to identify groups of patients according to their functional behaviour.

Results: Significant differences were found between the patients and control group for the RV function while the LV function remained mostly within normal limits.

When the RV function was considered, the control group and ASD patient group showed differences regarding the ARVD and PAH patients. On evaluating the RV/LV ratios, differences were found between the control group and the ASD group. In the PAH patients, LV function showed differences in relation to the rest of the groups.

Conclusion: RNV is a reliable clinical tool to evaluate RV function in patients with RV abnormality.

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Validación clínica de la ventriculografía isotópica planar en pacientes con disfunción del ventrículo derecho

R E S U M E N

Objetivos: La ventriculografía con radionúcidos (RNV) se puede utilizar para la evaluación de la función ventricular derecha, pero debe ser validada clínicamente en pacientes con patología específica del ventrículo derecho (RV) y con posible interacción del ventrículo izquierdo (LV).

Métodos: Tres grupos de 15 pacientes cada uno, con diagnóstico de displasia arritmogénica del ventrículo derecho (ARVD), hipertensión arterial pulmonar (PAH) o defecto del septum auricular (ASD) se comparan con un grupo de sujetos normales. Se valoran parámetros de ambos ventrículos por separado (fracción de eyeción: LVEF, RVEF y sincronismo intraventricular, cuantificado como la desviación estándar de la fase: LVPSD y RVPSD) así como la relación o interdependencia del RV con el LV (RV/LV volumen, LV/RV fracción de eyeción y sincronismo interventricular).

Se analizaron también todas las variables en conjunto para identificar grupos de pacientes según su comportamiento funcional.

Resultados: Se encontraron diferencias significativas entre los pacientes y el grupo control para la función del RV mientras que la del LV se mantiene dentro de los límites normales.

Palabras clave: Ventriculografía isotópica Ventrículo derecho Displasia arritmogénica del ventrículo derecho Hipertensión arterial pulmonar Defecto septal auricular Análisis de conglomerados

Abbreviations: ASD, atrial septal defect; ARVD, arrhythmogenic right ventricular dysplasia; IVD, interventricular dyssynchrony; LV, left ventricle; LVEF, left ventricular ejection fraction; LVPM, left ventricular phase mean; LVPSD, left ventricular phase standard deviation; LVSV, left ventricular stroke volume; PAH, pulmonary artery hypertension; RNV, radionuclide ventriculography; RV, right ventricle; RVEF, right ventricular ejection fraction; RVPM, right ventricular phase mean; RVPSD, right ventricular phase standard deviation; RVSV, right ventricular stroke volume; SOM, self organizing map; SPECT, single photon emission computed tomography.

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Introduction

There is widespread agreement on radionuclide ventriculography (RNV), in planar projection mode, as a reliable and robust modality for left ventricular function assessment. Despite some competition coming from more sophisticated single photon emission computed tomography (SPECT) approaches, whether myocardial perfusion gated-SPECT or blood pool SPECT, planar imaging remains, in many centres, the reference method and even a gold standard for the left ventricle (LV). The same degree of consensus is not achieved for the right ventricle (RV), due to various real or supposed drawbacks, some of them being specific for the RV: complex geometry and absence of a simple volume model, heterogeneity of contraction between ventricular chamber and pulmonary outflow tract, and others being common for both ventricles, namely heart chamber superimposition, changes of detector response with depth and tissue attenuation. Sometimes first pass imaging is proposed to circumvent some of these difficulties.2

After a several years experience we are convinced that planar gated blood pool imaging of both left and right ventricles used in daily practice is a valuable tool in many clinical circumstances, with significant impact on patient management, such as: contribution to the difficult diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD),1–12 planning of expensive drug therapy and follow-up of patients with pulmonary artery hypertension (PAH)13–15 and indication as well as post interventional control of patients with atrial septal defect (ASD)16,17 referred for transcatheter closure of the communication. The impact of an adequate evaluation of left and right cardiac functions in these diseases is not only medical but also socio-economical.

The aim of the present report is to demonstrate the clinical pertinence of findings in these three categories of patients compared to a normal reference group.

Methods

Study design

Patients with a known disease involving primarily the RV, mainly characterized by important right ventricular dilatation, but with possible secondary left ventricular implication, have been collected from a database of patients who were examined by RNV within a three years time period of stable technical condition – same gamma-camera and image acquisition and processing modalities – for planar gated blood pool studies. Raw image data have been reprocessed by the same operator at the same time for homogeneous computation of several variables, including data for RV or LV taken separately (ejection fraction and phase standard deviation) and data reflecting the right and left ventricular interaction (end-diastolic volume ratio, mean phase difference and stroke volume ratio). Coherence of results with the pathophysiology of the different right ventricular diseases included in the study has been verified and patient findings have been compared to values measured in a group of normal subjects. Finally, a computerized cluster analysis based on all the acquired functional parameters has been performed in order to attempt to classify patients into a number of groups with common functional behaviour.

Patients

Three groups of patients and one group of normal controls have been selected from our database over the defined study period.

The major inclusion criterion was a precise and clear-cut diagnosis, validated by the referring cardiologist. In this respect the limiting factor for the number of included patients was ARVD: in our population of 130 patients suspected at various degrees of this disease, only 15 cases could be unambiguously documented as being definitely ARVD. For the other, more frequent and more easily diagnosed diseases, and for the normal subjects, the same number of 15 cases in each group was also accepted in order to achieve balanced groups. Selection of patients for PAH and ASD was therefore conducted on the basis of consecutive cases with verified diagnosis until completion of the group.

Gender and age range for each group are given in Table 1.

Scintigraphic protocol

After blood pool labelling, “in vivo” red blood cells or “in vitro” human serum albumin, using a 700–800 MBq activity of 99mTc-technetium, planar electrocardiographically gated pictures (16 frames per cardiac cycle) have been acquired in the optimal (best septal LV and RV separation and cranio-caudal tilt for atrio-ventricular separation) left anterior oblique view on a General Electric DSTi gamma camera, equipped with a high resolution collimation with parallel holes. A total of 3200 Kcounts (an average of 200,000 counts per frame) were recorded for a time-period varying from 5 to 12 min, depending on the injected activity and the patient’s morphology.

A new image reprocessing (specific for the present study, without knowledge of the original results obtained at the time of clinical report) took place on a General Electric Vision post-processing station using the ECCAP software. Count based left (LVF) and right (RVF) ejection fractions were computed on semi automatically drawn (with possible manual correction) regions of interest, two regions (end-diastolic and end-systole for the LV), and one single region (end-diastole) for the RV. From these values was then derived the ejection fraction ratio LVF/RVF (a value usually higher than 1 since LVF is, at least in normal subjects, higher than RVF).

Using the same end-diastolic regions, background corrected ventricular counts were also collected in order to measure the volume ratio between RV and LV as: RV/LV volume ratio (in these patients with enlarged RV, the higher value over the smaller one to achieve also a ratio higher than 1). Combining the LVF/RVF ratio with the RV/LV volume ratio (the first divided by the second) yields RVSV/LVSV, the RV/LV stroke volume ratio (RVSV = RVF × RV volume and LVSV = LVF × LV volume). According to the physiological principle for cardiac output, i.e. right ventricular output equals the left one, in absence of valvular leaks or shunts, this ratio should be close to 1.

The same software allows temporal Fourier analysis using separately both right and left end-diastolic ventricular regions, leading to phase and amplitude image display and phase histogram construction.8–10 Histograms were characterized by their mean value (LVPM = left ventricular phase mean and RVPM = right
ventricular phase mean) and standard deviation (LVPSD = left ventricular phase standard deviation and RVPSD = right ventricular phase standard deviation). Phase standard deviations characterize the contraction heterogeneity for each ventricle (intraventricular dysynchrony) and the difference of the LV–RV mean phases measures the contraction delay between both ventricles (interventricular dyssynchrony = IVD).

Phases have been expressed in degrees (◦) on a 0–360◦ scale covering the R–R interval duration of the composite cardiac cycle. On this scale, the beginning of the cardiac cycle is 0◦, the location of end-systole is around 150◦ (variable with heart rate and the relative durations of systole and diastole) and the end of the cycle is 360◦.

Clustering method

Clustering is the segmentation of a population of patients into groups (called clusters) so that patients from the same cluster are more similar to each other than patients from different clusters. An important step in clustering is to measure, using a number of adequate variables, a distance between patients, from which the similarity of two patients is calculated.

In our study we used a method of clustering called “self organizing map” (SOM) which is based on the unsupervised learning algorithm of Kohonen.18–20 This method integrates several variables into the distance computation and uses a neighbourhood function to preserve the topological properties of the input data.

The first step to calculate a SOM is to define the number of required clusters (i.e. patient classes) and the computer will then assign randomly a data vector to each cluster in the population, with regard to the number of variables used for patient characterization.

In this method, the number of classes is therefore fixed by the user, and the system evolves towards an optimal segmentation after a number of iterations including a feedback process. One-dimensional SOM is used to reorder the elements on several axes of the network (i.e. for each variable). In this way the transition between groups becomes relatively smooth.

Statistical analysis

Data are presented as the mean ± standard deviation. Independent Student’s t-tests were used for comparison of variables between groups of patients. p-Values less than 0.05 were considered as statistically significant.

Results

Fig. 1 presents typical pictures for one case from each patient group and Fig. 2 gives detailed information for one ARVD case with all the variables measured for this patient.

Table 1 summarizes the results for the four groups of subjects and for the eight variables, directly measured variables (ejection fractions and phase standard deviations) or calculated variables (volume, ejection fraction and stroke volume ratios and mean phase difference = IVD). Statistically significant differences with respect to values for the normal subjects are written in bold italics.

Graphically for individual patients, Fig. 3 displays, for couples of variables, the distribution of patients according to their pathology: for isolated right ventricular data (Fig. 3a) for combination of right and left ventricular data (Fig. 3b) and left ventricular data alone (Fig. 3c).

Taking into account the eight variables together in the clustering process, Table 2 gives the correspondence between the clusters (groups 1–4) and the actual diseases of the patients. Using the same right ventricular variables than for Fig. 3a, Fig. 3d displays the patient data according to their belonging to clusters.

Table 1

<table>
<thead>
<tr>
<th>Group M/F</th>
<th>Age</th>
<th>RV/LV count ratio</th>
<th>RVEF (%)</th>
<th>LVEF (%)</th>
<th>LVEF/RVEF</th>
<th>IVD</th>
<th>RVPSD (◦)</th>
<th>LVPSD (◦)</th>
<th>LVSV/RVSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARVD</td>
<td>Mean</td>
<td>47</td>
<td>2.2</td>
<td>14.9</td>
<td>61.3</td>
<td>4.6</td>
<td>16</td>
<td>46</td>
<td>19</td>
</tr>
<tr>
<td>10 M/5 F</td>
<td>SD</td>
<td>16</td>
<td>0.7</td>
<td>4.7</td>
<td>7.7</td>
<td>1.6</td>
<td>11</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>PAH</td>
<td>Mean</td>
<td>65</td>
<td>3.6</td>
<td>14.3</td>
<td>55.6</td>
<td>4.1</td>
<td>16</td>
<td>61</td>
<td>30</td>
</tr>
<tr>
<td>10 M/5 F</td>
<td>SD</td>
<td>19</td>
<td>1.2</td>
<td>4.0</td>
<td>6.4</td>
<td>1.1</td>
<td>11</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>ASD</td>
<td>Mean</td>
<td>49</td>
<td>4.6</td>
<td>33.9</td>
<td>64.9</td>
<td>2.0</td>
<td>7</td>
<td>28</td>
<td>20</td>
</tr>
<tr>
<td>8 M/7 F</td>
<td>SD</td>
<td>17</td>
<td>1.6</td>
<td>5.2</td>
<td>5.1</td>
<td>0.3</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Normals</td>
<td>Mean</td>
<td>51</td>
<td>1.4</td>
<td>36.8</td>
<td>66.4</td>
<td>1.9</td>
<td>7</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>8 M/7 F</td>
<td>SD</td>
<td>6</td>
<td>0.2</td>
<td>6.4</td>
<td>5.6</td>
<td>0.4</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

Fig. 1. Typical end-diastolic (left) and end-systolic (right) blood pool pictures in three cases, one from each patient group, with enlarged right ventricle. Top: ARVD, middle: PAH and bottom: ASD.
Gated blood pool pictures
(16 frames / cardiac cycle)

Fourier phase analysis

RV / Phase histograms

Summary of functional variables

RV/LV count ratio = 2.3
RVEF = 16 %  LVEF = 72 %
LVEF/RVEF ratio = 4.5
RVMP = 142°  LVMP = 143°
IVD = 1°
RVPSD = 40°  LVPSPD = 20°
LV/RV stroke volume ratio = 2.0

Fig. 2. Summary of blood pool gated pictures, amplitude and phase images, LV and RV phase histograms and values of functional variables in one case of ARVD.

Discussion

Technical aspects

The question about the choice of planar imaging vs 3D SPECT imaging has been carefully discussed at the time of the study protocol design, both techniques being available in the institution.

The option of gated blood pool SPECT has been rejected, despite the existence of recent publications using this technique. Previously published experience using phase analysis on gated blood pool SPECT did not demonstrate a decisive superiority of SPECT compared to planar. The main reason was that tomographic slices are subject to partial volume effect when considering individual “thin” slices. On the corresponding 3D pictures, only the motion of the outline of the ventricular cavities has sense (endocardial wall motion). But Fourier analysis is basically obtained by modelling the changes in nuclear count rates, which supposes proportionality between counts and blood volumes. The proposed solution at the time of the previous mentioned study was to add together a series of individual “thin” slices in order to construct “thick” slices in the different tomographic orientations in which both ventricles were seen: horizontal long axis (4 cavities) and short axis. In fact we found obviously that “thick” short axis slices were not substantially different from left anterior oblique optimal projections and in further studies we decided to use planar projection rather than SPECT.

Phases are expressed in degrees from 0° to 360° rather than in time units (ms). This allows an easier comparison between patients since the values are then almost independent of the heart rate of patients.
Fig. 3. (a) Display of patients according to their diagnostic with regard to variables characterizing the right ventricular function: ejection fraction and phase standard deviation. ARVD and PAH are mixed on one side and ASD and normals have comparable values on the other side. (b) Display of patients for a couple of variables quantifying the right to left ventricular interdependence: volume ratio and ejection fraction ratio. Normals are clearly separated from ASDs patients whereas ARVD and PAH are partially mixed. C) Data concerning the left ventricle which are mostly within normal limits for all diseases, except some cases of PAH. (d) Display of clusters in the RV coordinates. Comparison with Fig. 3 which gives the diagnostics shows the mixture of ARVD and PAH within cluster groups 1 and 2.

**Choice of the clustering method**

A non-automatic classification of patients, using simply established limits of normality for the different variables could be an option for description of our scintigraphic results. Using an automatic clustering method has nevertheless significant advantages over a manual approach.

The Self Organizing Map (SOM) clustering method has been adopted for his stables results, which are independent of the initial patient distribution.

In order to give the same weight to every variable, each variable has been scaled on a 0–100 scale with 100 for the “best” value (the most normal one, i.e. the highest for ejection fractions and the lowest for phase standard deviation or volume indexes).

**Table 2**

Correspondence between 4 clusters resulting from computerized clustering of all patients and normals using the complete set of eight variables and their diagnosis. ARVD and PAH remain mixed in clusters 1 and 2 whereas clusters 3 and 4 show an acceptable separation of ASD patients vs other patients and normals.

<table>
<thead>
<tr>
<th></th>
<th>ARVD</th>
<th>PAH</th>
<th>ASD</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 1</td>
<td>8</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cluster 2</td>
<td>6</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cluster 3</td>
<td>1</td>
<td>2</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Cluster 4</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>15</td>
</tr>
</tbody>
</table>

**Coherence of right ventricle and left ventricle data in normal subjects**

Physiologically the RV output should be identical to the LV output and therefore the left over right stroke volume ratio should be equal to 1, at least in normal subjects. Different ratios can be found in cases of abnormal flows such as in valvular regurgitations or in septal defects with shunts.

The normal value found in this study (1.4 ± 0.3) is not the expected value of 1. This means that if it is assumed that LV data are correct, RV data are wrong and overestimate the LV/RV...
stroke volume ratio. Explanation of the increased ratio could be an underestimation of RVEF or an underestimation of RV volume, i.e. counts in the RV area of interest. Comparing with other imaging modalities, it is true that MRI, for instance, gives higher normal RVEF than RNV,\(^{21,22}\) in the range of 50%. If 50% would be the normal RVEF instead of our measured 36.8%, using all the other RNV data, the stroke volume ratio would be 0.95, a value very close to 1. Clues for technical explanations of this discrepancy are the fact that RVEF measurement in our methodology takes place on one single area of interest, the same for end-diastole and end-systole, whereas LVEF is measured on separate end-diastolic and end-systolic areas of interest, and also the fact that the background value is taken at the border of the LV, which is relatively far from the RV.

Pathophysiological interpretation for each patient group and possible functional separation of patients groups

ARVD. The right ventricle is dilated, but the RV/LV volume ratio is not as high as for PAH or ASD. This can be explained by the fact that visually the left ventricle seems of normal size in ARVD whereas in PAH and ASD not only the RV is dilated but also the LV is noticeably reduced in size, and the volume ratio increases for both reasons. RVEF is severely reduced and RVPSD is high. The corresponding values for LV are normal. Some IVD is possible. There is a problem with the stroke volume ratio, which is higher than normal, Extrapolating to the case of ARVD, underestimation of ejection fraction for technical reasons cannot completely explain a factor as high as 2.2 between left and right stroke volumes. There is probably also an underestimation of RV volume, perhaps due to the presence of RV dyskinetic areas in this disease.

PAH. In these patients, the volume ratio is coherent with the ejection fraction ratio, and the stroke volume ratio is comparable to the normal one, with the same moderate underestimation of RVEF. Visually, the elevated volume ratio results not only from enlarged RV but also from reduced LV, which is different from ARVD. Values of RVEF are in the same range than those in ARVD, and LVEF are still within the normal limits. The main difference is the left ventricular contraction heterogeneity with LVPSPD significantly increased compared to the other diseases and normals.

ASD. Patients show the same elevated volume ratio with a large LV and a reduced RV. Both LVEF and RVEF are normal as well as all the phase variables. In these cases, the stroke volume ratio varies in the opposite way, with a higher RV stroke volume than the LV one. This clearly results from left to right atrial shunt which creates a right ventricular volume overload.

Fig. 3 displays some possibilities of partial separation using couples of parameters.

In Fig. 3a, ARVD and PAH on one side and ASD and normals on the other side are well separated using RV data alone.

Biventricular data as displayed in Fig. 3b are able to distinguish ASD from normals, which were totally mixed in Fig. 3a.

Considering LV data alone (Fig. 3c), there is some incomplete separation between PAH and the three other categories.

These results motivated the use of clustering taking into account all the eight available variables together. Fig. 3d presents the same data than Fig. 3a for patient clusters. Values of Table 2 show that this promising method did not fully separate all diseases, ARVD being mixed in the same proportion in two clusters whereas ASD and normals are well separated in the two other clusters.

Possible impact on patient management

RNV is a simple and accurate method for cardiac functional characterization. Addition of RV variables to the corresponding LV variables and quantifying the functional interaction of both ventricles may present some diagnostic utility, as in ARVD, but in most cases, when the disease is well known, the utility of studies is more for follow-up of patients, whether before and after intervention, as it is the case in ASD, or for assessment of medical therapy, for instance in PAH.

In all these cases, the knowledge of the RV function is of crucial importance, since the LV functions is usually quite normal in these diseases.

The socioeconomical consequences of an adequate evaluation of biventricular function are heavy, considering the ages of patients, around the fifties, the possible vital risks, sudden death for ARVD, or severe handicap for PAH, and the cost of interventions, as it is the case in ASD closure.

Compared to other modalities, RNV is more precise than echography\(^{15,22,23}\) and cheaper or easier to perform than CT and MRI. Our evaluation study demonstrates that the RV is accessible as well as the LV, and in addition, both ventricles can be evaluated in the same time, without additional radiation.

Limits of the study

All patients included in this study had a priori diseases associated with dilated right ventricles. Our results cannot be extended to cases with normal right ventricular volumes and the clinical utility of RNV in these situations has still to be demonstrated. The imaging modality, planar projection, is probably not the most accurate method for precise measurement of right ventricular functional variables in the context of diagnosis for other RV diseases which do not show RV dilatation.

Conclusion

RNV is certainly not the gold standard for RV assessment, as it is for the LV. The processing method used in this study, based on one single RV area of interest compared to the two areas for the LV, may be a reason for some underestimation of RVEF compared to other imaging modalities. The complex shape of the RV may also be a cause of lack of accuracy.

Despite these limits, the method remains easy to perform and is clinically useful in specific settings, when the dilatation of the RV chamber compensates, at least partially, the technical uncertainties, giving finally a clinically acceptable value.

The proposed examples, collected from three diseases with dilated RV, demonstrate that the results are consistent with the physiopathology of the diseases.

Conflict of interest

The authors have no conflicts of interest to declare.

References


