Development of an image processing algorithm for the diagnosis of chronic thromboembolic pulmonary hypertension

P. Cara[1], A.P. Seiffert[1], P. Pilkington[2], A. Gómez-Grande[2], E.J. Gómez[1,3], P. Sánchez-González[1,3]

[1] Grupo de Bioingeniería y Telemedicina, ETSI Telecomunicación, Centro de Tecnología Biomédica, Universidad Politécnica de Madrid, Madrid, España; paula.caraa@alumnos.upm.es, {aseiffert, egomez, psanchez}@gbt.tfo.upm.es

[2] Servicio de Medicina Nuclear, Hospital Universitario 12 de Octubre, Madrid, España; patrick_pilkington@yahoo.com, adolfogomez@gmail.com

[3] Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina, Madrid, España

Abstract

A severe variant of pulmonary hypertension is a chronic thromboembolic pulmonary hypertension (CTEPH) that is related to acute pulmonary embolism. The current diagnosis is performed by visual analysis of single-photon emission computed tomography (SPECT) ventilation and perfusion images. A mismatch of defects that are only present in the perfusion image confirms the diagnosis. This paper presents an algorithm to diagnose CTEPH based on the comparison of the volumes extracted from both SPECT images. The algorithm is designed to also differentiate between cases of CTEPH and a respiratory pathology. A total sample of 32 patients is divided into three groups depending on their diagnosis: (1) reference, (2) CTEPH and (3) respiratory pathology. Reference values of segmentation thresholds and lung volumes are obtained from the first group. These volumes are then used to define thresholds for the classification of the cases of groups two and three. After segmenting the SPECT images and calculating the volumes of ventilation and perfusion, these thresholds are applied to determine the diagnosis. Even though a small patient database is used, the results indicate that the quantitative analysis of SPECT ventilation and perfusion images can support the diagnosis of CTEPH.

1. Introduction

Pulmonary hypertension (PH) is a group of diseases defined as an increase in mean pulmonary arterial pressure (PAP) greater than 25 mmHg at rest. It is characterized by persistent constriction or blockage of the arteries, hindering blood flow to the lungs and causing chronic PAP elevations. The increase in PAP induces a right cardiac overload, which weakens the cardiac muscle, generating right ventricular pressure dysfunction [1, 2].

Chronic thromboembolic pulmonary hypertension (CTEPH) is a severe variant of PH that is caused by chronic occlusion of the pulmonary arteries and arterioles by organised blood clots, followed by progressive vascular remodelling of small unobstructed vessels [3]. It is also accepted that CTEPH is related to acute pulmonary embolism (PE). In Spain, the diagnosed incidence is reported at 3.4 cases per 100,000 population per year. Data from 5 European countries show incidences ranging from 66 to 101 cases per 100,000 population per year [4].

Currently, the diagnosis is carried out through a comparative visual analysis of single-photon emission computer tomography (SPECT) ventilation and perfusion (V/Q) images. To assess the presence of pulmonary thromboembolism, areas of hypoperfusion not concordant with areas of hypoventilation are identified. The existence of defects, of triangular morphology with peripheral base, in the pulmonary parenchyma of the pulmonary perfusion image, which are not present in the pulmonary ventilation image, confirms the diagnosis of CTEPH [5].

The interpretation of the images allows to determine the presence of CTEPH or other respiratory pathology, according to the following criteria [3]:

- Positive CTEPH diagnosis: Presence of at least one segmental defect or two sub-segmental perfusion defects not consistent with ventilation in pulmonary SPECT images.
- Negative CTEPH diagnosis: Normal perfusion in which the edges of the lung are preserved or presence of concordant defects in both the ventilation and perfusion.
- Respiratory pathology: Presence of defects in the ventilation image that are not concordant with the perfusion.

This work proposes a new image processing algorithm for the diagnosis of CTEPH and to differentiate it from respiratory pathologies. The algorithm is based on the analysis of SPECT ventilation and perfusion images and the guidelines for the visual inspection of the images defined by the European Association of Nuclear Medicine (EANM) [3] and the European Society of Cardiology (ESC)/European Respiratory Society (ERS) [5].

2. Materials and Methods

2.1. Subjects

This retrospective study is conducted from a database of patients whom, between June 2017 and May 2019, were hospitalized with suspected CTEPH, as an initial diagnosis, at the *Hospital Universitario 12 de Octubre* in Madrid, Spain. For the final study group, 32 patients areselected based on the following inclusion criteria: (1) suspicion of CTEPH as an initial diagnosis at first appearance, after remitting symptoms such as chest pain and dyspnea, (2) SPECT image tests of pulmonary V/Q and TC of pulmonary arteries, and (3) confirmation diagnosis of old CTEPH with or without recent improvement in pulmonary perfusion. The exclusion criteria are: (1) absence of any of the tests described above, (2) V/Q SPECT study with artefact,

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(3) inconclusive or indeterminate studies, and (4) radiotracer accumulations in specific points of the pulmonary parenchyma during the ventilation study caused by the presence of excess mucus.

The sample of 32 patients is divided into three groups according to the diagnostic criteria given by physicians specialised in nuclear medicine from the *Hospital Universitario 12 de Octubre* (see *Table 1*). The three groups are: (1) reference, (2) CTEPH, and (3) respiratory pathologies. The reference group is composed of 10 patients that do not show any non-concordant defect in the pulmonary V/Q SPECT images, so they are assumed as patients with normal lung function or patients with concordant defects in both images. The diagnosis of CTEPH is confirmed in 12 patients. The 10 patients that compose the third group are diagnosed with some type of respiratory pathology including chronic obstructive pulmonary disease (COPD) and chronic bronchitis, or some type of PH without thromboembolism.

	N	Gender (m/f)	Age (y ± SD)
Reference	10	2/8	61.40 ± 9.74
CTEPH	12	8/4	61.50 ± 13.44
Respiratory pathology	10	2/8	70.10 ± 13.51
Total	32	12/20	64.16 ± 12.82

Table 1: *Demographics of the study population*

2.2. Image Acquistion

SPECT images are provided by the department of nuclear medicine of the *Hospital Universitario 12 de Octubre*. The images were acquired using a SKYLight gamma camera (Philips, Amsterdam, Netherlands) with a Low Energy All-Purpose (LEAP) collimator. During the 360° circular rotation of the gamma camera in "step and shoot" mode, 64 projections were acquired, each with a duration of 30 seconds. Ventilation studies were performed after airway administered ^{99m}Tc-Technegas. The aerosol was inhaled by the patients for 15-20 minutes through deep, slow breaths with 5-second pauses between each breath. For the pulmonary perfusion study, 5 mCi of technetium macro aggregated albumin (^{99m}Tc-MAA) was administered intravenously. The images had a matrix size of 64×64 and were processed at a JETStream Workspace version 3.0 (Philips, Amsterdam, Netherlands) workstation.

2.3. Image Analysis

SPECT images are analysed using MATLAB R2018b (The MathWorks, Inc., Natick, Massachusetts, USA). All analyses are performed for each lung separately due to the anatomical differences between the left and right lung [6]. Discordant perfusion defects are quantified using a threshold-based segmentation of the lung volume in both ventilation and perfusion images. The segmentation includes all voxels above a specified percentage of the maximum intensity present in the SPECT images. High difference values between both volumes (V_{V-P}) are defined as being indicative of said discordant defects. Image analysis is divided into two steps: (1) calculation of reference values, and (2) application in pathological cases that correspond to the second and third group of the subject database to validate the algorithm. The methodology is shown in *Figure 1*.

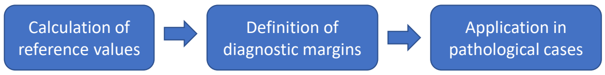

Figure 1: *Methodology*

Calculation of reference values. In order to obtain reference values of normal or concordant lung volumes, at first the images of the reference group are analysed. A total of 4 reference values per lung are calculated based on the images. These are:

- Optimal segmentation thresholds for the ventilation images.
- Optimal segmentation thresholds for the perfusion images.
- Mean V_{V-P} of all the subjects of the reference group (Mean($V_{V-P,\ ref}$)) for the optimal segmentation thresholds.
- Minimum V_{V-P} of all the subjects of the reference group (Min($V_{V-P,\ ref}$)) for the optimal segmentation thresholds.

The four optimal segmentation thresholds are determined by iteratively segmenting the lungs with different values defined between two thresholds and calculating the volumes. The images are segmented until the lowest average of volume differences of the group was obtained. Finally, the lowest V_{V-P} is then calculated employing the optimal segmentation thresholds determined previously.

Application in pathological cases. In order to classify a pathological case, the Mean($V_{V-P,\ ref}$) and Min($V_{V-P,\ ref}$) values are used to establish normal margins in order to determine the diagnosis of these pathological cases. Moreover, once the optimal segmentation thresholds are obtained, these values are applied to calculate V_{V-P} of pathological patients.

Firstly, to establish the difference between patients with a CTEPH diagnosis and patients that present some type of respiratory pathology, the sign of V_{V-P} needs to be taken into account. In the same way that the volume of perfusion decreases in patients with CTEPH, in patients with respiratory pathologies the decrease in volume occurs in the ventilation phase. Therefore, a positive value of V_{V-P} is indicative of CTEPH and a negative value represents a lower volume in the ventilation image than in perfusion.

Once V_{V-P} of the patient is obtained, Mean($V_{V-P,\ ref}$) and Min($V_{V-P,\ ref}$) are compared to the absolute values of V_{V-P} to determine the existence of CTEPH or respiratory pathology. Both values are taken into account as the volumes obtained from the ventilation and perfusion images are not exactly the same even in normal cases or when presenting concordant defects. Thus, in order to establish a V_{V-P} large enough to indicate a positive CTEPH diagnosis or the presence of some type of respiratory pathology, the following conditions are defined:

- Volume difference values between ventilation and perfusion, which are above the mean reference $V_{V\text{-}P}$ value, indicate a positive diagnosis.
- Volume difference values between ventilation and perfusion, which are below the mean reference $V_{V\text{-}P}$ value and above the minimum reference $V_{V\text{-}P}$ value, indicate suspicion of CTEPH or respiratory pathology, whose diagnosis cannot be ruled out but will require a complementary visual analysis to confirm the positive diagnosis of CTEPH.
- Volume difference values between ventilation and perfusion, which are below the minimum reference $V_{V\text{-}P}$ value, indicate a negative diagnosis.

Finally, the validation is carried out by applying the algorithm to the pathological cases. The segmentation of the lungs is performed, and the volumes are calculated. The difference $V_{V\text{-}P}$ is then calculated for each lung and the previously defined classification methodology is applied to obtain a diagnosis. To evaluate the accuracy of the algorithm we calculated the sensitivity and the false negative rate (FNR) of the classification because we applied the algorithm in each group separately. A case is considered correctly classified if the algorithm cannot rule out a positive diagnosis.

3. Results and Discussion

3.1. Calculation of reference values

The search for the optimal segmentation thresholds is realized between 14% and 22% increasing the thresholds by 1% in each iteration. The upper and lower thresholds are defined after a visual analysis of the segmentation of the lungs in the ventilation and perfusion images with percentages. Lower and higher values result in a segmentation that does not represent correctly the lung volume. The optimal segmentation thresholds obtained after the grid search are shown in *Table 2*.

	Left Lung	Right Lung
Ventilation	15%	21%
Perfusion	21%	18%

Table 2: *Optimal segmentation thresholds*

In *Table 3*, the reference volume values are shown. These correspond to the segmentation of the images of the reference group using the pairs of segmentation thresholds shown in the previous table.

	Left Lung	Right Lung
Mean ($V_{V\text{-}P,\,ref}$)	328.82 cm^3	816.04 cm^3
Min ($V_{V\text{-}P,\,ref}$)	119.01 cm^3	466.84 cm^3

Table 3: *Reference volume values*

In *Figure 2* and *Figure 3*, an example of the segmented SPECT ventilation and perfusion images is shown. These correspond to a 58 years old woman who presents normal lung function. Both images show relative homogeneous uptake patterns. The complete lung volume was segmented in both images and visually they are similar. This results in low $V_{V\text{-}P}$ values that are used to represent normal lung function.

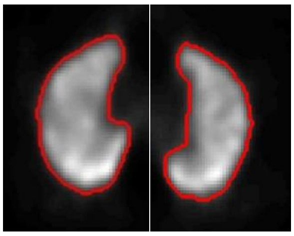

Figure 2: *Segmented SPECT ventilation image of a subject of the reference group.*

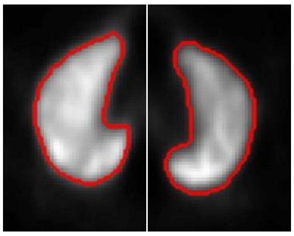

Figure 3: *Segmented SPECT perfusion image of a subject of the reference group.*

3.2. Application in pathological cases

After obtaining the reference volumes, these are applied to the conditions that are described in the previous chapter (see *Table 4*). The absolute value of $V_{V\text{-}P}$ is used as the conditions are applied to both pathological groups. To determine if the case is a potential CTEPH or respiratory pathology, the sign of $V_{V\text{-}P}$ is first evaluated.

Diagnosis	Left Lung	Right Lung
Positive	$\lvert V_{V\text{-}P}\rvert > 328.82$ cm^3	$\lvert V_{V\text{-}P}\rvert > 816.04$ cm^3
Cannot be ruled out	328.82 cm^3 > $\lvert V_{V\text{-}P}\rvert$ > 119.01 cm^3	816.04 cm^3 > $\lvert V_{V\text{-}P}\rvert$ > 466.84 cm^3
Negative	$\lvert V_{V\text{-}P}\rvert < 119.01$ cm^3	$\lvert V_{V\text{-}P}\rvert < 466.84$ cm^3

Table 4: *Quantitative diagnostic scale*

The optimal segmentation thresholds are used to obtain the values of $V_{V\text{-}P}$ for each patient of groups two and three, that is, patients that present discordant defects in the images. With these values, the diagnosis is determined by the algorithm for each lung separately based on the conditions defined in *Table 4*. An example of a 55 years old woman diagnosed with CTEPH and presenting defects in the SPECT perfusion image is shown in *Figure 4*. Regions of hypoperfusion can be identified in the perfusion image. Due to the lower uptake, these regions are not segmented by the algorithm as the voxel values are beneath the segmentation threshold.

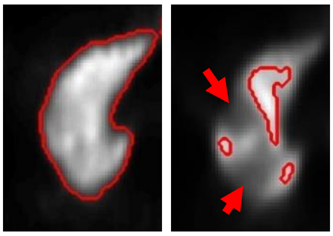

Figure 4: *Patient of the CTEPH group showing a normal ventilation image (left) and CTEPH-typical defects (arrows) in the perfusion image (right).*

The results of the classification of the pathological cases is shown in *Table 5*. Overall, a sensitivity of 63.64% and an FNR of 36.36% are obtained.

	CTEPH	Respiratory pathology	Both groups
Sensitivity	0.67	0.6	0.64
FNR	0.33	0.4	0.36

Table 5: *Classification results*

Analysing the results separately, it can be observed that the algorithm performs slightly better in the CTEPH group. In this case, the sensitivity is 66.67% (8/12). Out of the 8 cases that are classified correctly, 2 yield a “Cannot be ruled out” result. This represents a 16.67% of the cases. As is mentioned in section 2, this result does not imply that patients do not suffer from CTEPH, but the defects present do not affect the total volume of pulmonary perfusion enough, in order to establish a reliable diagnosis. In these cases, patients require a visual analysis of the images to confirm or rule out the diagnosis. It is noteworthy that only 1 of the patients classified as positive with certainty is a woman. This can be explained by the fact that the reference values are more representative of the female lung anatomy due to the demographics of that group (see *Table 1*). The reference volumes and thresholds tend to favour a positive diagnosis in men due to the anatomical differences between the lungs of both genders (male lungs are slightly larger than female lungs) [7]. Finally, 4 of the 12 patients with a positive CTEPH diagnosis are falsely classified resulting in an FNR of 33.33%.

On the other hand, 60% (6/10) of the cases that are diagnosed at the hospital with a respiratory pathology are also correctly classified by our algorithm. In this case, a positive diagnosis cannot be ruled out in 1 case by the algorithm. Out of the 6 correctly classified cases, 4 are women and 2 are men. It is important to note that the group only comprised 2 men. The same explanation of the demographics of the correctly classified cases as in the case of the CTEPH patients applies to this group. Regarding the false negative cases, 2 are classified as “Cannot rule out CTEPH”. This indicates that the volume obtained from the perfusion image is larger than the ventilated volume and not the other way around as would be expected in cases of a respiratory pathology. Both cases were diagnosed with chronic obstructive pulmonary disease.

Future works include a revision of the cases included in the reference group. Firstly, the database could be expanded with more cases to increase the accuracy of the reference values. Moreover, the reference group is principally composed of women (8/10). This leads to reference values that are more representative of the female gender. Therefore, an improvement would be to divide the reference group into two, one of women and another one of men. This could further improve the accuracy of the reference values and result in them being more representative of each gender. Furthermore, due to the limited availability of SPECT ventilation and perfusion images of subjects with normal lung function, patients with concordant defects in both images are included in the reference group. However, a healthy control group could be formed with cases that present normal lung function.

Despite the limitations in terms of the reduced number of patients, the algorithm is able to diagnose CTEPH correctly in two thirds of the patients. Moreover, it shows good capacity to differentiate CTEPH from respiratory pathologies.

4. Conclusions

CTEPH is a severe variant of pulmonary hypertension and caused by the chronic occlusion of the pulmonary arteries by organised blood clots. It is currently diagnosed by the visual inspection of SPECT ventilation and perfusion images. An algorithm is developed to diagnose patients who present CTEPH or a respiratory pathology. The algorithm is based on the processing of SPECT ventilation and perfusion images extracting the respective volumes. The difference between the volumes of ventilation and perfusion was defined as the quantitative metric to determine the diagnosis. This diagnosis was performed using reference values obtained from a group of patients who present normal lung function or concordant volumes in both images. The results show that the quantitative analysis of SPECT ventilation and perfusion images in patients with CTEPH could complement the visual analysis performed in the clinical practice.

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