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Clinical Kidney Volume Measurement Accuracy Using NEFROVOL

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***Abstract*— In case of Autosomal Dominant Polycystic Kidney Disease, kidney volume provides an indicator of disease progression. To estimate such growth, ultrasound is a safe and low cost imaging technique, albeit limited to regular shape organs. We developed a new measurement method with skin silicon templates to obtain parallel and equidistant images of the kidney, as a series of transverse sections. With NEFROVOL software, nephrologists are able to contour kidney boundaries, reconstruct a 3D renal representation and calculate its volume, including extremely irregularly shaped. We conducted a phantom study with sweet potatoes, volunteers and patients with transplanted or enlarged kidneys. The volumetric error decreases from 22% to 15% as the number of sections increases from 4 or 5 to 6 or 9 for patients and potatoes respectively. Best precision was estimated with 9 sections for 15 cm sweet potatoes and 6 sections for 11 cm healthy kidneys. The best skin template is one with two positions for the internal frame, with one section every 1.5 cm.**

Keywords*— *Autosomal Dominant Polycystic Kidney Disease, Ultrasound, Kidney Volume, Volume Measurement, NEFROVOL.

I. Introduction

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most prevalent and life threatening monogenic disorder. Characterized by cyst formation and enlargement in kidney principally, it affects 1 in 500 to 1000 births [1], [2], [3]. It is caused by two known mutations: PKD1 gene (85% of cases) and PKD2 gene (remaining 15%). The PKD1 mutation is associated to a more severe disease, with earlier age at diagnosis, increased prevalence of hypertension and earlier onset of end-stage kidney disease (ESKD) than PKD2 mutation (54 years mean age of onset of ESKD with PDK1 and 74 with PKD2) [1], [2]. Renal function decline is related to renal enlargement, making kidney and cyst volume a strong predictor of disease evolution [3]–[6]. Higher rates of kidney enlargement lead to a more rapid decline in renal function [6]. This was the original motivation to develop a non invasive method to measure kidney volume [7].

In order to obtain kidney volume measurement, three imaging techniques are used: Magnetic Resonance Imaging (MRI), Computed Tomography (CT) or Ultrasound (US). Moreover, the screening and diagnosis of ADPKD in any particular individual relies on imaging criteria depending on his/her age, his/her genetic background or family history and upon the number of cysts [1], [2], [8].

MRI is a precise technique with high resolution in all directions. MRI is not suitable for carriers of any metallic device, claustrophobic persons or patients who cannot keep still or lie down (in which cases sedation or anaesthesia may be required). MRI may include the injection of a gadolinium-based contrast agent, asociated to nephrogenic systemic fibrosis, especially for persons suffering from kidney disease [9]. When it comes to volume measurement, it will give a detailed data set and provide a good accuracy. There is also a variety of visualization software on the market to automatically calculate kidney volume [10] from MRI. The use of MRI with manual contouring shows highly reproducible results, $R^2 = 1$ for intra-observer and $R^2 = 0.996$ for inter-observer agreement [11] and a standard error of less than 5% [12].

CT scans give high resolution and good estimation of kidney volume as well, but expose the patient to ionizing radiation and possibly also requires contrast agent injection.

With respect to US, images displayed on the screen are of a lower resolution and sharpness, and look somewhat “blurred”. This is due to the physical limitations of the US technique [13]. US images are moreover very much operator-dependent. Usual clinical practice to measure kidney volume by US adopts the ellipsoid formula: an approximation of volume is obtained from the 3 axes (x, y & z) measured by the operator in different scan orientations. The ellipsoid volume formula is:

Length * Lateral diameter * Antero-posterior diameter * π/6

It is difficult to have reproducible and reliable measurements with harmless US procedures (which can be repeated due to its non toxicity), even for normal kidneys. Bakker et al. find that the ellipsoid formula under-estimates by 24% the volume of 20 cadaveric pig kidneys (range 5 - 48%) using US in comparison to fluid displacement as gold standard [14]. Kim and coworkers find a 16% underestimation of healthy kidney volume measured by US ellipsoid compared to CT voxel count method [15]. The ellipsoid method is therefore biased towards roughly 20% lower kidney volume, as there appears to be a systematic error, both for pig series and healthy volunteers. Even considering its systematic underestimation, the ellipsoid method is only applicable to roughly regular kidneys, while irregular shapes such as those found in progressing ADPKD do not allow to define "ellipsoid axes" in a reliable and reproducible way.

For follow-up, in order to avoid unnecessary CT originated ionizing radiation and to reduce MRI costs, clinical nephrologic teams recommend periodic US imaging [1], [2], [8]. But there are no clinically available instruments to fulfil the requirements of an innocuous, simple method. We have therefore developed **NEFROVOL** (name derived from the contraction of "volume" and "nephrology" in Spanish) since 2013 [7], a low cost, non-invasive solution to estimate kidney volume from US imaging. We have suggested for the first time a combination of parallel and equidistant US images in DICOM format [16] in order to generate 3D organ models and calculate the resulting volume [17]. Our software, **NEFROVOL**, allows users to import DICOM images from any US equipment. The present paper reports on subsequent versions of hardware templates for **NEFROVOL**, as well as a formal estimation of its accuracy.

II. NEFROVOL CHARACTERISTICS

NEFROVOL is a method and a software along with a skin guide, to record US sections and later combine them into an estimated volumetric representation. This 3D object represents the kidney volume. All US equipment are compatible with **NEFROVOL**, as long as they include a series of images of kidney sections along its main axis, each image included in a separate DICOM file. In addition, every patient being followed clinically will have different procedures performed over the years. An Electronic Clinical Record (ECR) output is created with the details of a single measurement of the 3D volumetric reconstruction. In case more than one exploration is available, the output of **NEFROVOL** describes the volume change in a time graph for each kidney [7].

To build the kidney volume, the user is asked to contour the organ in every image of the set of parallel scans. The 3D model is generated from the boundaries, a mesh is created and saved as an STereoLithography file (STL) to be used by 3D printers or other software. The images and results are recorded as an item in the patient ECR in Clinical Document Architecture (CDA) format [18]. The 3D printed model could be used as an additional element in patient-physician interactions, either in full or reduced scale.

A. *NEFROVOL Software*

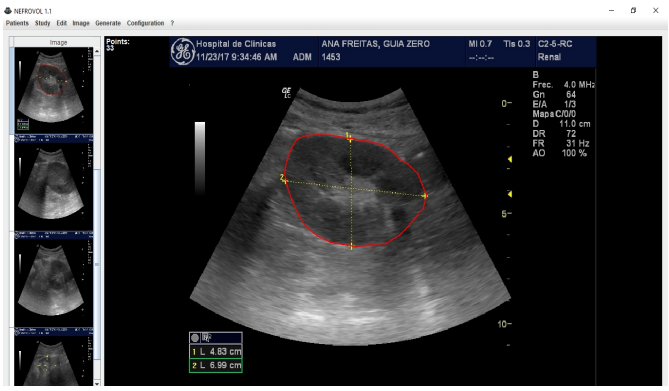


Fig. 1. **NEFROVOL** software screen. Note the contour drawn by the user on the image being processed and the series of US kidney sections on the left.

Visually, the software is divided into three sections, one for the menu; the second one contains the DICOM images already imported; and the third one is the interactive screen for the user to draw image contours (Fig.1). The user defines in each imported image the kidney contour, by marking points, united by straight lines by **NEFROVOL** software. Clinical and physiopathologic expertise is important here, as any error at this stage will inevitably affect volume measurement later.

To obtain a mesh, these points are used, three at a time, as vertexes of triangles encompassing two adjacent contours. The set of all such meshes represents the kidney, except for the two extremities. To construct them, **NEFROVOL** uses a projection along the renal axis of the centre of gravity of the last contour at half the distance between two adjacent slices.

For volume reconstruction, the **NEFROVOL** software uses two distinct methods, the Volumetric Pixel method and the Layered Convex Hull method [7].

The Volumetric Pixel method is based on a 3D matrix of [X, Y, Z] coordinates of the cloud of points conforming the volume. A voxel is defined as the elementary unit of volume (a cube of $1mm^3$). For every possible voxel of the space, the method checks if it includes any point of the solid. To determine whether a voxel is included in the kidney structure, a line is drawn (computationally) from an external origin of X, Y, Z space to the centre of the voxel. The intersections of this vector with all the triangles of the two-contour mesh are calculated. If the vector crosses the boundary of the solid an odd number of times, the voxel is included in the kidney, otherwise if the vector crosses the boundary an even number times, the last action of the vector was to exit the solid, so it is classified as external to the volume. Summing up all "odd" voxels gives a volume estimation of the kidneys, irrespective of its irregular, reentrant, convex or concave shape. The quantity of voxels that include a kidney point, multiplied by the volume of one voxel turn out to be an estimation of the renal volume by this method.

As the determination of the intersections with the kidney of all possible voxels is time consuming, we therefore apply a combination of the two methods: Volumetric Pixel and Layered Convex Hull Method. The Volumetric Pixel method is used only for the points included in one layer at a time. Each kidney layer was previously obtained with the Layered Convex Hull Method as a pair of contours. By doing so, we keep both the precision of the Volumetric Pixel Method and the speed of the Layered Convex Hull Method.

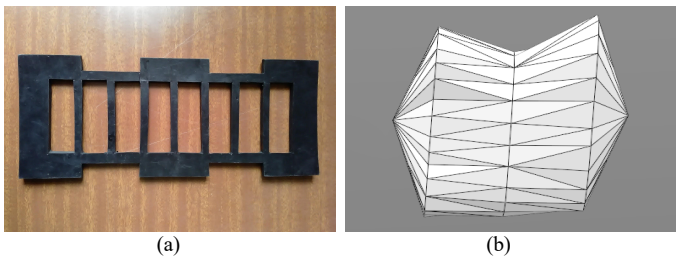
The Layered Convex Hull method considers clouds of points in horizontal layers. Each layer is structured as a convex container defined by Delaunay triangles [19]. Delaunay triangulation is such that no point is inside the circumcircle of any triangle, it maximises the minimum angle of all the angles of the triangles and avoids sliver triangles. In our case, triangulation is created from point clouds in one plane, where vertices are point clouds and there are no inner points. The rectilinear sides link the point clouds without crossing any other links. The total volume is the sum of all convex areas multiplied by the layer height.

For both extrapolated extremities of the volume, we use the pyramid formula ($\mathbf{V} = \mathbf{A_b} \times \mathbf{h} / 3$) where $\mathbf{A_b}$ is the pyramid base area and **h** is the height, which is equal to half the period of the skin guide.

B. Skin guides

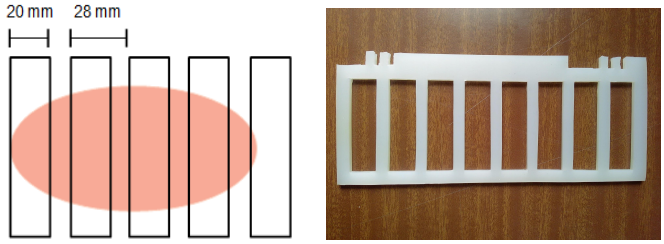
In order to ensure the equidistance and parallelism of US images, we developed guides (or skin templates) with slots for the transducer C2-5 RC of the General Electric (GE) scanner LOGIQ C5 PREMIUM [20].

The first skin guide (or template) developed for **NEFROVOL** was a silicon rectangle with 8 slots for the US transducer (Fig. 2 (a)) [7]. The dimensions of each slot were 75×25 mm in order to receive the C2-5 RC transducer, separated by 5 mm, the resulting "period" being therefore 30 mm. The thickness was 7 mm. The use of silicon allows to obtain a lightweight, hypoallergenic guide which may be sterilized. Several problems occurred with this first guide. The material was too stiff to properly adapt to the roundish morphology of the patient. Slices or sections are separated 30 mm from each other and considering that healthy kidney is on average 110 mm long [21], we were able to obtain a maximum of 4 sections. The resultant 3D kidney model lacked accuracy, due to a gross simplification of its shape in space (Fig. 2 (b)).



(a) (b)

Fig. 2. (a) **NEFROVOL** original skin guide, 280 x 125 mm, adapted for transducer C2-5 of GE LOGIQ C5 equipment. (b) Kidney captured and reconstructed by **NEFROVOL** with 3 sections and two extreme points extrapolated at half the period distance.



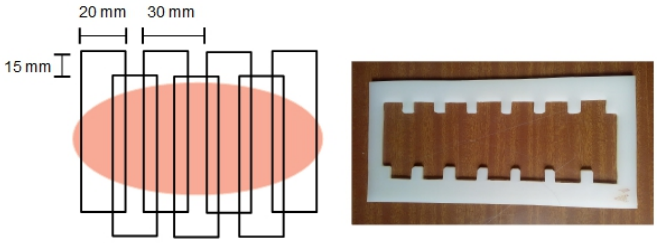
(a) (b)

Fig. 3. **NEFROVOL** A0 skin template to be applied to the skin (a) kidney profile to show transducer positioning (the kidney is visible until the fourth slot and no more in the fifth) and (b) practical silicon guide A0, 235×105 mm in dimensions giving an US image every 28 mm.

To increase the precision, we devised new templates with two and three times the number of sections for the same guide length. We thus designed three 5 mm flexible silicon guides. We used the same type of silicon, except its greater flexibility (5 mm thick instead of 7 mm) to better adapt itself to the morphology of the patient by bending smoothly over the abdomen or the back of the patient.

One of the three new guide models named A0, is a 235×105 mm silicon rectangle with 8 slots of 75×20 mm (Fig. 3). The slots are designed so as to guide the US operator when affixing the transducer on the patient´s skin. Therefore each slot has the exact dimensions of the transducer, in our initial case a C2-5 transducer connected to a GE LOGIQ C5 equipment. Each slot is separated 8 mm from the next. This distance is a trade-off between keeping the guide resistant enough and aiming at the minimum possible distance in order to get as many slice as possible. Guide A0 gives a US slice every 28 mm, smaller than the original 30 mm. This distance is taken into account by **NEFROVOL** software to build 3D volumes in space to scale.

The second silicon guide developed, called A1, is a rectangle of 252×110 mm with 14 slots (75×20 mm) arranged in zig-zag (Fig. 4). Guide A1 has alternate notches on each side of the inner rectangle. The notches on either side are 20 mm apart, taken from one axis of even to the axis of odd transducer positions. The US transducer is therefore affixed on one or the other side of the template, following a zig zag for the sequence of sections. A1 gives one slice every 15 mm, for a better spatial resolution with respect to A0.



(a) (b)

Fig. 4. A1 type **NEFROVOL** guide with alternating axis: (a) kidney profile to show transducer positioning with seven sections where the kidney is visible and (b) silicon guide A1, 252×110 mm giving a US image every 15 mm.

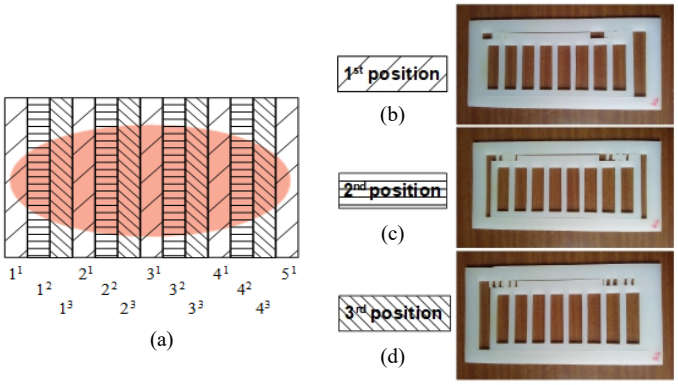


Fig. 5. A2 skin template: (a) Schematic representation of a kidney exploration using guide A2 in three positions ¹, ² and ³. Spatial order to enter in **NEFROVOL** is $1^1\ 1^2\ 1^3\ 2^1\ 2^2\ 2^3\ 3^1\ 3^2\ 3^3\ 4^1\ 4^2\ 4^3\ 5^1$ while US scanning is obtained in the sequence $1^1\ 2^1\ 3^1\ 4^1\ 5^1\ 1^2\ 2^2\ 3^2\ 4^2\ 1^3\ 2^3\ 3^3\ 4^3$. (b) Skin Template A2 with inside guide in position 1, (c) in position 2 and (d) in position 3.

The third guide, named A2, is a little bit more complex to operate (Fig. 5). It has two different parts, the inner one (similar to guide A0) moves inside the framework of a larger guide which is a rectangle of 298×145 mm (outside dimensions). Three positions are available, each one separated from the previous by 9.3 mm in the direction of the kidney axis. The step of the guide is 28 mm, to be used in three positions. The physician places the outside guide in one skin position and does not move it for the rest of the exploration. The inner guide is then placed in the first position to obtain all the sections the kidney is visible in. Next, the inner guide is moved one notch to allow a second series of kidney sections. Finally the inner guide is placed in the third position to obtain the last series of sections. When the US images are imported by **NEFROVOL** into its working memory, the user re-orders the images in the right sequence starting by the first images of every position. With A2 template, every image obtained is therefore 9.3 mm apart from each other. Note that the sequence of images has to be re ordered from the original three interwoven vectors into a spatially contiguous list of sections.

Clinical US exploration was convenient to undertake, using any of the three silicon guides, except for double or thrice the work for A1 and A2 respectively, due to the number of images taken and later processed.

III. NEFROVOL VOLUME RESULTS

A. Sweet Potatoes Volume Measurement

First of all, we conducted a phantom study with 4 sweet potatoes. In a small tank, we glued the sweet potato to the bottom of the tank with hot silicon and then we filled up the tank with physiological serum (0.9% sodium chloride). Without the hot silicon glue, the sweet potato would float making all repeated measurements difficult. The sweet potatoes are thus available to be US scanned 3 cm below the surface, simulating physiological position. We conducted a US exploration with A0, A1 and A2 to study guide influence on volume estimation. After that, we measured their volume by fluid displacement in a full tank of water as gold standard volume measurement.

TABLE I. VOLUME ERROR OF SWEET POTATOES

	Guide A0	**%**	**Guide A1**	**%**	**Guide A2**	**%**	**Reference volume**
	cm³		***cm³***		***cm³***		***cm³***
Sw. Potato 1	154	-3%	191	20%	146	-9%	160
Sw. Potato 2	147	38%	129	22%	120	13%	106
Sw. Potato 3	196	33%	165	11%	133	-10%	148
Sw. Potato 4	215	14%	175	-7%	156	-17%	188
Average		**21%**		**11%**		**-6%**	
‖Average‖		**22%**		**15%**		**12%**	

‖X‖ represents the average of the absolute values.

B. Kidney Volume Measurement

We selected a sample of 6 people: 2 healthy volunteers, 2 patients with a transplanted kidney and 2 ADPKD patients. The protocol has been submitted to the ethics committee of the Hospital de Clinicas and all (patients and volunteers) signed an informed consent.

All patients underwent a routine 2D ultrasound examination by a nephrologist. For transplanted patients, and due to the position of the transplanted kidney just below the skin, the US scans were obtained ***antero-posterior*** to maximize image accuracy. For volunteers and ADPKD patients, US scans were obtained ***postero-anterior***. APDKD patients also had an abdominal CT-scan, available in their clinical records, less than one year before the **NEFROVOL** procedure. The CT scan allowed us to calculate the kidney volume as reference to evaluate measurement precision.

TABLE II. VOLUME ERRORS USING **NEFROVOL** ON PATIENTS

Alias	**Med Cond**	**Guide A0**	**%**	**Guide A1**	**%**	**Guide A2**	**%**	**Ref. volume**
		cm³		***cm³***		***cm³***		***cm³***
P1	T	236	27%	164	-11%	119	-36%	185
P2	T	180	43%	147	17%	137	9%	126
P3	H	181	23%	134	-9%	131	-11%	147
P4	H	82	-31%	80	-32%	100	-16%	118
P5	A	280	1%	285	3%	228	-18%	278
P6	A	198	8%	138	-25%	117	-36%	184
Average			**12%**		**-10%**		**-18%**	
‖Average‖			**22%**		**16%**		**21%**	

P1 to P6 are patients and volunteers

Medical Condition (Med. Cond.) T= transplanted patient, H= healthy volunteer and A = ADPKD patient.

The reference volume for patients with medical condition T and H was calculated with the ellipsoid formula, and for ADPKD a volume estimation by CT scan. Patient P6 is compared to the ellipsoid formula.

‖X‖ represents the average of the absolute values.

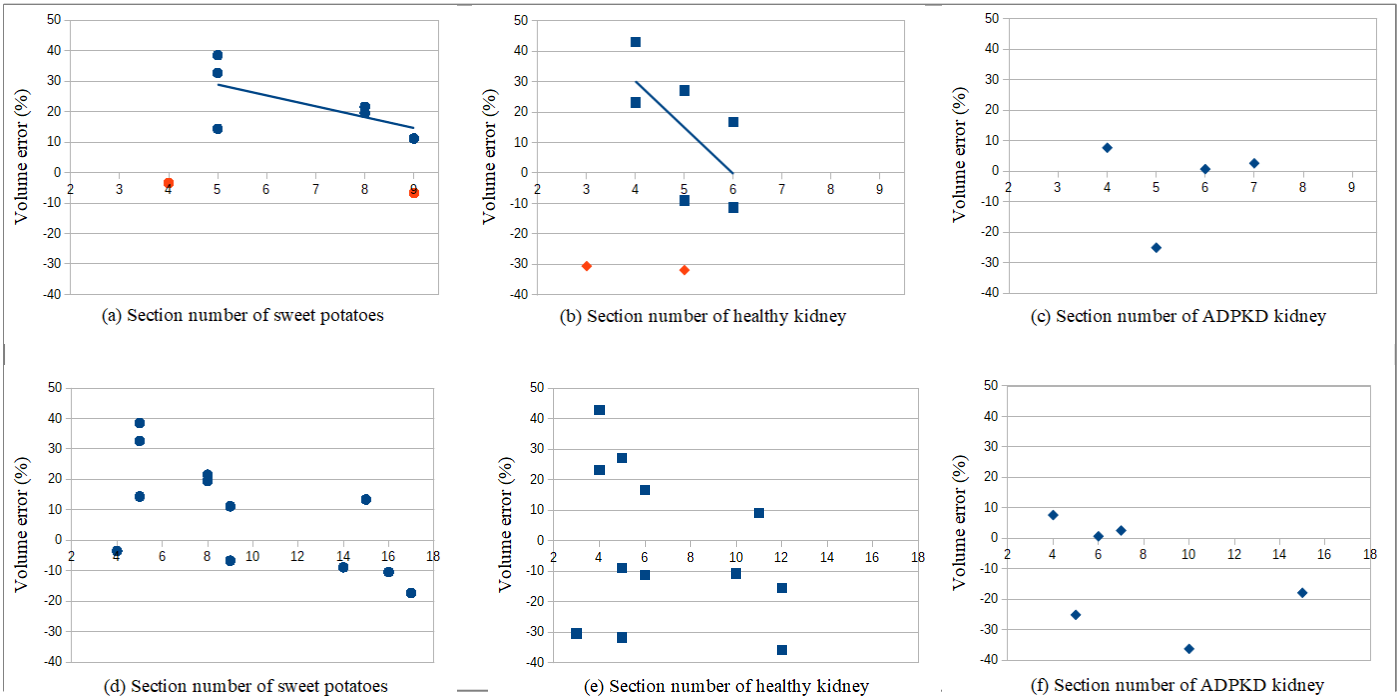


Fig. 6. Volume error graphs according to the number of sections: until 9 sections to include A0 and A1 template for (a) sweet potatoes, (b) healthy kidney, (c) ADPKD kidney. Outlier points in red are not taken into account for the linear regression. $R^2 = 0.39$ for (a) and $R^2 = 0.41$ for (b). Second row of graphs (d, e and f) shows all sections for sweet potatoes, healthy kidneys and ADPKD enlarged kidneys. Points above 10 sections are only possible with A2 template, with its 9.3 mm period, as opposed to 28 and 15 mm of A0 and A1.

IV. Errors and Number of Sections

The estimated error is expected to decrease as the number of sections increases, i.e. as A0, A1 and A2 skin templates are used. Fig. 6 (a) (b) and (c) show this error becoming better for sweet potatoes, healthy volunteers and ADPKD patients respectively, limited to 9 slots. The volumetric error overall decreases from about 22% to 15% as the number of sections increases from 4 or 5 (A0 template) to 6 or 8 (A1 template) for patients and potatoes respectively.

The second row of graphs (Fig. 6 (d), (e) and (f)) shows the volume error for each and all measurements taken with A0, A1 and A2, including -of course- the A0 and A1 of the first row. The decreasing error observed for increasing number of sections ((a) and b)) is not seen for ADPKD patients (c) for whom surprisingly the error rate is independent of the skin template used. Using the A2 template, the error tends to underestimate the volume.

V. Discussion and Conclusion

NEFROVOL fulfils the goal of a measurement technique and is now available as a new instrument for irregular kidneys such as those of ADPKD patients. This confirms previous results obtained which gave errors of 15% for irregular vegetables and less than 10% for simple parallelepipedic volumes [7], [17]. Hammoud and coworkers selected in 2015 the best axis for the ellipsoid method according to the widest transverse section in the axial plane, and obtained average errors of 9% when compared to CT techniques for early ADPKD patients [22]. This group could not fare better than 9% with respect to CT image processing, with no reference to gold standard volumetric measurements by water displacement.

The results of the present paper show that by multiplying by two or by three the number of slots (A1 and A2 skin templates respectively), **NEFROVOL** error can be lowered to a figure close to 10%, according to the graphs of Fig. 6 (a) and (b). For ADPKD patients, the error appears even smaller (Fig. 6 (c)), a clear advantage with respect to the ellipsoid technique, used only for normal or early ADPKD cases.

By using parallel sections of **NEFROVOL,** the work of the medical personnel increases if compared to the "*ellipsoid three axis measurements*". But then, the ellipsoid method is highly inappropriate for ADPKD patients due to the "fractal-like" shape of their kidneys. With **NEFROVOL** a 10% error rate can reasonably be expected, if a detailed measurement protocol is followed with the appropriate skin templates. This promising order of magnitude for ADPKD patients kidney volume estimation (10%) allows to envision a future when clinicians will have, with **NEFROVOL**, a tool for long term non invasive follow-up. The measurement protocols will have to be further developed based on the present preliminary and innovative results.

Increasing the number of sections to be manually drawn (or defined automatically in the near future) increase the potential sources of error, in addition to representing an additional burden for the clinician. The optimal trade-off appears to be somewhere around 6 sections for kidneys (i.e. the A1 skin template), as shown in Fig. 6.

The A2 skin template is prone to additional manipulating errors due to the fact that the inner frame can adopt three positions, compared to the single frame of A0 and the zig-zag frame of A1. Practical considerations confirm therefore that a better "section resolution" of three intertwined templates (A2) does not necessarily produce better overall measurement accuracy than the zig-zag A1. It must be kept in mind as well that the A1 skin template uses alternate frame positions sideways, while A0 and A2 have definite slots (not sideways notches) to house the transducer longitudinally.

ADPKD is a disease characterized by an average of 5% yearly volume increase over decades of life [4], [5]. This is why a 10% measurement error is barely good enough in a follow-up tool, unless repeated measurements are low pass filtered to highlight general trends. This trend is ultimately what clinicians expect of **NEFROVOL** so as to be able to anticipate patient condition and nephrological functionality to adopt the most appropriate decisions for patient management.

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