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● *Original Contribution*

HIGH-RESOLUTION ULTRASOUND VISUALIZATION OF PACINIAN CORPUSCLES

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Abstract—The aim of this study was to evaluate the possibility of visualizing Pacinian corpuscles in the palm of the hand with high-resolution ultrasound (HRUS). In this prospective study, HRUS with a high-frequency probe (22 MHz) was used. The palms of two fresh cadaveric hands were screened for potential Pacinian corpuscles. Still ultrasound images and dynamic video sequences were obtained. In five regions with large amounts of suspected Pacinian corpuscles, tissue blocks were excised and histologically processed, and corresponding slices were compared with ultrasound images. Further, the transverse diameters of five Pacinian corpuscles, at the level of the metacarpal heads in the palm, were assessed on both sides (in total 100) in healthy volunteers. On ultrasound, Pacinian corpuscles presented as echolucent dots in the subcutis, adjacent to digital nerves and vessels and located 2−3 mm beneath the surface. On histologic sections, these echolucent dots corresponded to Pacinian corpuscles with respect to their position and topographic relationships. The mean transverse diameter for all volunteers was 1.40 ± 0.23 mm (range: 0.8−2.2 mm). This study confirms the ability to reliably visualize Pacinian corpuscles with HRUS, which contributes to our basic understanding of ultrasonographically visible subcutaneous structures and may enhance the diagnosis of pathologies related to Pacinian corpuscles. (E-mail: peter.brugger@meduniwien.ac.at) © 2018 World Federation for Ultrasound in Medicine & Biology. All rights reserved.

Key Words: **Ultrasonography, Pacinian corpuscle, Histology, Painful nodule, Palm.**

INTRODUCTION

Pacinian corpuscles are one of the four major types of cutaneous mechanoreceptors located in the deep dermis and subcutaneous tissue, and are especially prevalent in the palm and fingers (Johnson et al. 2000). They are extremely sensitive, rapidly adapting sensory receptors that respond to vibration and pressure (Johnson 2001; Vega et al. 2009). A possible consequence of this function is the perception of distant events through transmitted vibrations (Brisben et al. 1999).

Reports on Pacinian corpuscle pathologies are rare. Most of the cases reported are neuroma formation (sometimes described as Pacinian hypertrophy or hyperplasia) (Cho et al. 2012; Garcia et al. 2015; Irie et al. 2011; Jones and Eadie 1991; Mahipathy et al. 2015; Sedy and Skalna 2015; Zanardi et al. 2011) or involvement in Dupuytren's disease (Akyurek et al. 2000; von Campe et al. 2012; Yenidunya et al. 2009) and neurofibromatosis (MacLennan et al. 1999; Yan et al. 2006). Patients may present with an unspecific swelling or a tender papule. Clinical symptoms could be point tenderness, decreased sensation and slight to severe pain. To date, except for some studies that described the visualization of Pacinian corpuscles and the demonstration of a Pacinian neuroma—all detected with magnetic resonance imaging (MRI)—imaging played no role in the evaluation of normal or pathologic findings (Laistler et al. 2018; Szeles et al. 2001; Wadhwa et al. 2014).

High-resolution ultrasound (HRUS), using high-frequency linear probes, offers excellent tissue differentiation, but comes with the disadvantage of reduced tissue penetration. This, however, makes HRUS ideal for the examination of superficial structures. Because the number of palmar Pacinian corpuscles in the hand has been reported to be 3−20 per square centimeter (Jones and

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Eadie 1991; Lang-Stevenson 1984), with a size ranging from 0.2 to 5 mm (Jones and Eadie 1991; Kim et al. 2018; Lang-Stevenson 1984; Sedy and Skalna 2015), and because of their cutaneous location, we hypothesized that Pacinian corpuscles could be detected by ultrasound with high-frequency probes.

The identification of Pacinian corpuscles by HRUS, therefore, may (i) enhance basic ultrasound knowledge of possibly visible subcutaneous structures and, thus, improve the differential diagnosis, and (ii) improve diagnostic assessment in patients with unclear, painful, papule-like swelling in the hand or fingers. Therefore, the aim of this study was to confirm the correct identification of Pacinian corpuscles by HRUS, with histologic correlation in anatomic specimens, and provide the first measurements of its transverse diameter in healthy volunteers.

METHODS

This prospective study was approved by the local ethics committee of the Medical University of Vienna (EC No. 1529/2015) and was conducted in June 2016.

Ultrasound in anatomic specimens

High-resolution ultrasound and histologic sections were performed on two randomly selected hands in legal custody of the Center of Anatomy and Cell Biology, Medical University of Vienna.

Ultrasound in healthy volunteers

Ten healthy volunteers were recruited *via* notices at the Department of Biomedical Imaging and Image-Guided Therapy and by word-of-mouth. Written, informed consent was obtained from all volunteers. The inclusion criterion was age >18. Exclusion criteria were known polyneuropathy, known myopathy, chronic disease known to cause peripheral neuropathy and previous hand surgery.

Five visible Pacinian corpuscles at the level of the metatarsal heads in the palm were assessed on both sides (in total 100). Measurements of the maximum transverse diameter were obtained using the platform software of LOGIQ e.

Ultrasound technique

High-resolution ultrasound examinations were conducted using a GE LOGIQ e (GE Healthcare, Wauwatosa, WI, USA) ultrasound platform with a high-frequency probe (GE L10-22-RS: active area, 8×20.3 mm; bandwidth, 20 dB; 10−22 MHz; central frequency, 17 MHz; depth range, 0.5−4 cm; elements, 128). For Pacinian corpuscle assessment, probe settings were as follows: frequency, 22 MHz; frame rate, 64; focal length, 2 mm. All HRUS examinations were performed by a radiologist with 5 y of experience in peripheral nerve imaging (G.R). First, all palms were screened for possible Pacinian corpuscles, from the level of the distal radioulnar joint to the fingertips. Because of the superficial location of Pacinian corpuscles, the image depth was adjusted to a maximum of 0.5−1 cm. Special attention was required to angulate the probe to avoid anisotropy and to ensure that the presumed corpuscles were in full view and not distorted in the image. After identification of potential Pacinian corpuscles in anatomic specimens, five areas that measured approximately 2×2 cm with the most Pacinian corpuscles in each palm were defined. The ultrasound probe was positioned perpendicular to the surface. Then, pins were inserted medial and lateral to the midline markings of the probe. Examinations were documented using photographs and both still images and dynamic video ultrasound sequences. Probe positioning and pin placement are illustrated in Figure 1.

Histologic assessment

Both hands were from an 84-y-old female donor. Immediately after HRUS, the hands were perfused with 4% phosphate-buffered paraformaldehyde and then dehydrated through a series of graded alcohols. Rectangular blocks consisting of cutis and subcutis were then excised from the hardened specimens and embedded in paraffin. The pins were removed and replaced by a colored thread to indicate the US midline. Special care was taken to orient the blocks accordingly before embedding in paraffin. Corresponding to the US imaging plane, 15-μm-thick sections

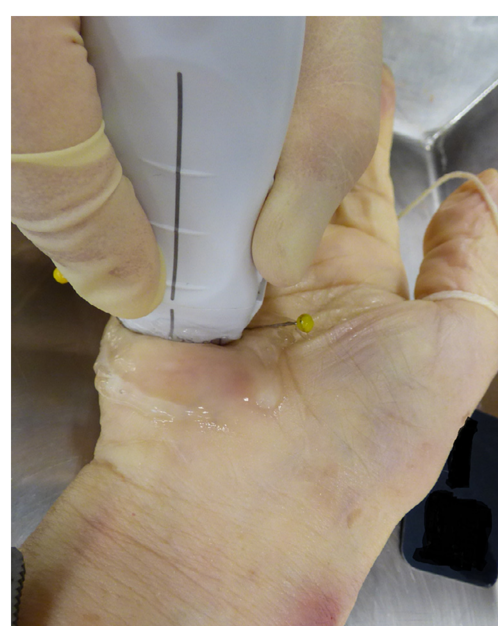

Fig. 1. Probe positioning and pin placement at an area with a large amount of Pacinian corpuscles.

were cut perpendicular to the surface on a microtome (Leica Jung RM2055, Nussloch, Germany), mounted on glass slides and stained with hematoxylin and eosin.

Statistical analysis

Descriptive statistics were performed using SPSS Statistics for Windows Version 22.0.0.2 (IBM, Armonk, NY, USA). Metric data in healthy volunteers (Diameter of Pacinian corpuscles) are expressed as the mean ± standard deviation and range (minimum to maximum).

RESULTS

HRUS−histologic correlation

Sonographically, the Pacinian corpuscles appeared as echo-free black dots, sometimes with some weak, hyperechoic, somewhat long internal structures. They were found adjacent to nerves and vessels in the palmar subcutis, located 0.2−0.3 cm beneath the surface. Their classic histologic lamellar structure was not depictable with HRUS. In all histologic sections, the Pacinian corpuscles corresponded to the echolucent dots in terms of their position and topographic relationship to the nerves and vessels (Figs. 2 and 3; Supplementary Video S1, online only).

Ultrasound in healthy volunteers

Three females and seven males (mean age, 26.2 y; age range, 23−32 y) were included in the study. Assessment of Pacinian corpuscles was possible in all volunteers. Sonographically, Pacinian corpuscles presented an echogenicity similar to that in anatomic specimens. The mean transverse diameter for all volunteers was 1.40 ± 0.23 mm (range, 0.8−2.2 mm). Pacinian corpuscles measured 1.40 ± 0.22 mm (range, 0.8−2.2 mm) on volunteers' left palm and 1.40 ± 0.24 mm (range, 0.8−2.2 mm) on volunteers' right palm.

DISCUSSION

In this work, we confirmed the possibility of reliable identification of Pacinian corpuscles with HRUS, as matched with histologic findings.

Histologically, Pacinian corpuscles can be observed in the deep layer of the corium, below sweat glands in the palmar subcutaneous fat, and at the sides of the proximal and middle phalanges adjacent to the periosteum (Cauna and Mannan 1958). Corpuscles usually cluster near nerves and vessels in the metacarpophalangeal and phalangeal regions of the three central digits (Akyurek et al. 2000). The corpuscles usually measure 1−1.5 mm in the long axis, number 3−5 per square centimeter and usually have fewer than 20 concentric lamellae (Fraitag et al. 1994; Lang-Stevenson 1984). A hypertrophied Pacinian corpuscle may include 35−60 concentric lamellae with an increased diameter of the

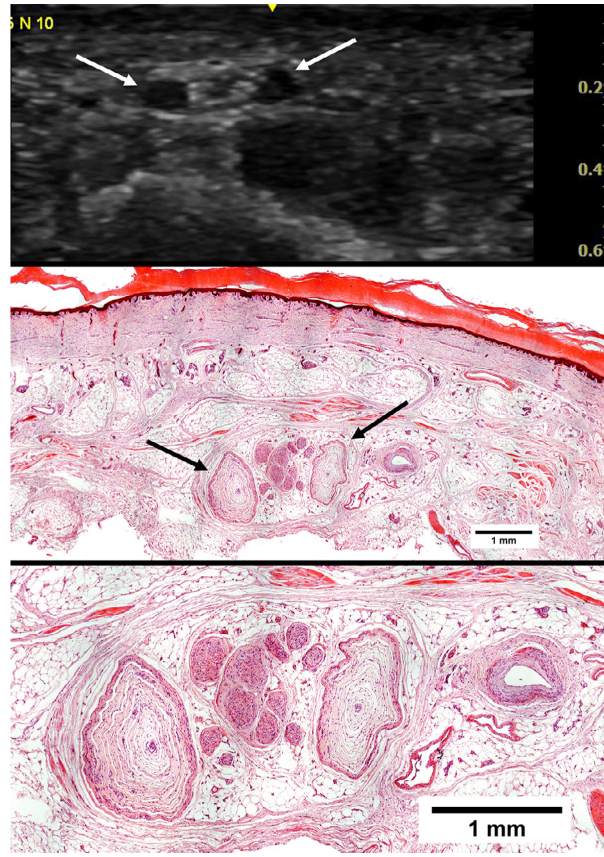

Fig. 2. High-resolution ultrasound images of Pacinian corpuscles and their histologic correlates. On the top image, the right scale indicates the depth of the ultrasound image in centimeters. The ultrasound image reveals two echolucent dots (marked with *arrows*), indicating Pacinian corpuscles adjacent to a common palmar digital nerve (indicated as a fascicular structure on the ultrasound and histologic images).

corpuscle (*e.g.,* 1.6−5 mm) (Lang-Stevenson 1984, Stark et al. 1998), and there could be up to 20 corpuscles per square centimeter (Akyurek et al. 2000). It has been estimated that there are a total of 300−800 Pacinian corpuscles in the hand (Brisben et al. 1999; Yenidunya et al. 2009).

Because of the rapid improvements in ultrasound technology over the past decade, HRUS offers excellent resolution and contrast and is also able to depict superficial structures with diameters <1 mm (Riegler et al. 2017). This allows for assessment of very small anatomic structures and may, therefore, enhance patient management and our *in vivo* understanding of physiologic and pathologic processes. However, it may confuse a clinician and lead to false interpretation of imaging findings.

In this study, we used a 22-MHz ultrasound probe that provides an axial resolution of ~0.1 mm and a lateral resolution of ~0.15 mm. This may explain why Pacinian corpuscles are detectable with high-frequency ultrasound

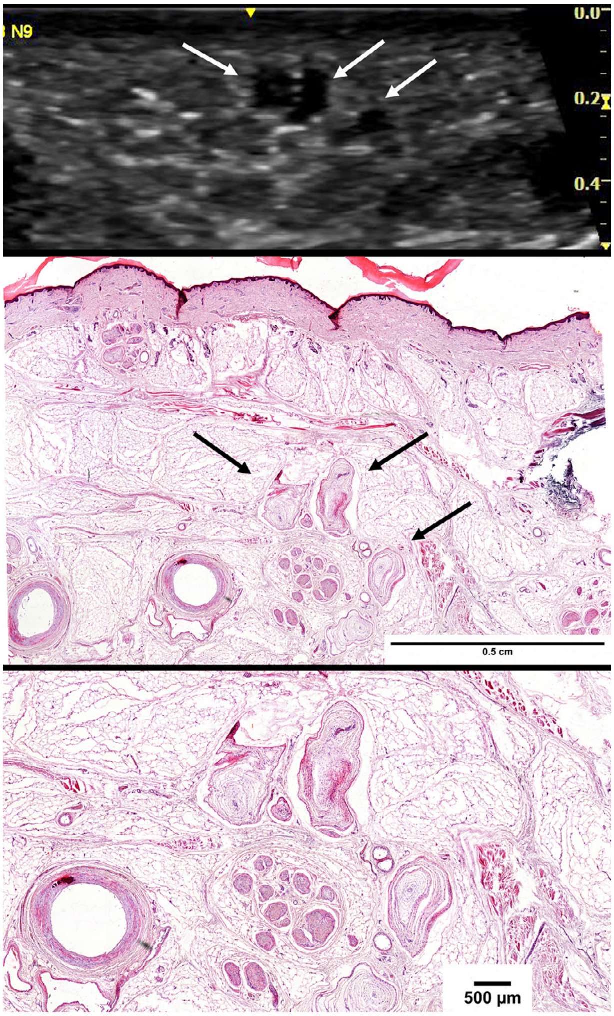

Fig. 3. High-resolution ultrasound images of Pacinian corpuscles and their histologic correlates. On the top image, the right scale indicates the depth of the ultrasound image in centimeters. The ultrasound image reveals three Pacinian corpuscles (marked with *arrows*) on the top and right in relation to a common palmar digital nerve (indicated as a fascicular structure on the ultrasound and histologic images).

probes. Their hypo-echoic appearance may be attributed to the fact that more than 92% of the corpuscle is water (Cherepnov and Chadaeva 1981). Nevertheless, the internal structure of Pacinian corpuscles could not be visualized. This inability to visualize the internal appearance may be the result of two possible factors: The distance between different lamellae within the corpuscle seems to be 0.02−0.1 mm (Vega et al. 2009) and may, therefore, not be detectable by HRUS; and/or the impedance differences between a lamella and the connective tissue in the corpuscle are too low to produce measurable echoes with the probe used.

In the present study, most of the visible Pacinian corpuscles were located at the level of the metacarpal heads adjacent to the palmar digital nerves, which is in line with observations by Stark et al. (1998). In this region, there are many different anatomic structures and pathologies, which may confuse the physician performing the ultrasound. Because of a hypo-echoic appearance that is potentially similar to that of other structures (Zhu et al. 2011) and the proximity of a Pacinian corpuscle to a palmar digital nerve, a Pacinian corpuscle may easily be misinterpreted as a small neuroma formation of a palmar digital nerve. Differentiation between a digital nerve neuroma and a painful Pacinian corpuscle (neuroma) may better guide a patient's further treatment and therefore, patient comfort. Both pathologies may benefit from surgery (Jones and Eadie 1991; Yan et al. 2006). Although a palmar digital nerve neuroma is usually surgically treated by neurotomy, a Pacinian neuroma should be resected (Jones and Eadie 1991; Yan et al. 2006).

Because of similar echogenicity, differentiation between a small, non-compressible ganglion or a tendon sheath cyst formation and a Pacinian corpuscle may cause another diagnostic and therapeutic problem. In some cases, steroid injections are therapeutically performed in ganglia or tendon sheaths. However, because steroid injections may provoke or worsen permanent pain as a result of Pacinian corpuscle irritation (Jones and Eadie 1991), they should be avoided. Thus, high-resolution ultrasound may guide therapy in these cases. Other differentials include neurofibromas and glomus tumors (Jones and Eadie 1991). Neurofibromatosis I and II are known to be associated with painful Pacinian hyperplasia (Yan et al. 2006) and must be distinguished from a "true" Pacinian neurofibroma, which exhibits corpuscle-like differentiation in a myxoid stroma and is not related to neurofibromatosis (MacLennan et al. 1999). In most cases, a neurofibroma has higher echogenicity on ultrasound compared with a Pacinian corpuscle and is larger (MacLennan et al. 1999; Reynolds et al. 2004). Nevertheless, in some cases, it may not be possible to distinguish these two entities. Very rarely, a glomus tumor may be associated with Pacinian hyperplasia. The ultrasonographic appearance of a glomus tumor is hypo-echoic with almost always visible intranodular vascularization, which may distinguish it from a Pacinian corpuscle (Catalano et al. 2017; Yan et al. 2006).

Several distinct abnormalities of Pacinian corpuscles have been described. One accepted classification was proposed by Rhode and Jennings (1975) using four types: type A, single, enlarged subepineural corpuscle; type B (most common), a grape-like cluster of normal-sized Pacinian corpuscles attached to the digital nerve by a fine filament; type C (extremely rare), slightly enlarged corpuscles arranged in tandem beneath the epineurium; type D, hyperplastic Pacinian corpuscles arranged along the entire length of a digital nerve. However, because of the rarity of these abnormalities and the paucity of histologic information, there are no accepted histologic parameters with respect to what constitutes hyperplasia and which pathology requires further therapy (Jones and Eadie 1991). Painless nodules that measure approximately 4 mm were found in blind patients, which the authors postulated were secondary to an increased demand for fine touch (Lang-Stevenson 1984) or to painless Dupuytren's disease (Akyurek et al. 2000; Yenidunya et al. 2009). In most cases, patients had a previous trauma, localized pain, occasional numbness and, sometimes, sensory changes and nodular swelling (Jones and Eadie 1991; Yan et al. 2006). Surgical excision of the painful Pacinian corpuscles appears to be the best therapeutic option and seems to be almost uniformly curative (Jones and Eadie 1991; Yan et al. 2006). In this regard, high-resolution ultrasound may potentially help clinicians to determine differential diagnosis (*e.g.,* tendon sheath ganglia) or to support the possibility of a Pacinian corpuscle pathology (*e.g.,* size >5 mm). Nevertheless, because there are no accepted histologic parameters for what constitutes Pacinian pathologies, as described above, further studies are needed to define clear histologic and radiologic criteria for such conditions.

With respect to other imaging modalities, MRI has been reported to have a great potential to visualize Pacinian corpuscles (Laistler et al. 2018). Therefore, both imaging modalities (MRI and ultrasound) may further enhance the diagnosis of Pacinian corpuscle pathologies in the future. Because US provides a more accessible imaging choice, high resolution and faster imaging, and MRI may provide a better overview of the area of interest, we think the two imaging modalities are complementary and have the potential to provide information on Pacinian corpuscle pathologies in the future.

This study has several strengths and limitations. Its strengths include the first-time use of HRUS for the assessment of Pacinian corpuscles and confirmation of the findings with histologic correlation. Its limitations include that only two cadaveric hands were used in this evaluation for rigorous histopathological validation, because such a validation could not be performed on the healthy volunteers. Nevertheless, the data obtained by this study are based on five regions of interest correlated with high-resolution ultrasound, which strengthens the results. Moreover, a potential distortion of the cutis and subcutis as a result of the (necessary) pressure exerted by the ultrasound probe could have led to slightly different positioning of Pacinian corpuscles in the images when matching the histologic and ultrasound images. A further limitation is that only a small number of *in vivo* samples from healthy volunteers were obtained. Therefore, further *in vivo* studies on healthy volunteers and patients are needed to provide a definitive statement about the diagnostic reliability of *in vivo* Pacinian corpuscle assessment with HRUS.

CONCLUSIONS

This study confirms the ability to reliably visualize Pacinian corpuscles with HRUS in anatomic specimens and healthy volunteers, and therefore, we encourage its use. Further studies are needed to assess the value of HRUS in diagnosing Pacinian corpuscle pathologies.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.ultrasmedbio.2018.08.001.

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