

# Vascular corridor for implantation of a stimulating electrode into the nucleus anterior thalami - an experimental study

## Vascular corridor for implantation of the anterior thalamic nucleus stimulation electrode - an experimental study

### Summary

*Aim:* Stimulation of the anterior thalamic nucleus (ATN) may be considered in patients with pharmacoresistant epilepsy without the possibility of other surgical therapy. The ATN projects into the lateral ventricle as the tuberculum thalami, with the v. thalamostriata laterally and the choroid plexus with the v. chorioidea superior medially forming the border and corridor for electrode implantation. The aim of this study was to study the width of this vascular corridor in terms of implantation safety and seizure reduction (best when stimulating the anterior nucleus). *Setting and Methods:* after dissection of both hemispheres of the specimens with intracranial vessel injection, the tuberculum thalami (ATN) was identified with a vascular border. Corridor width measurements were taken 2, 4 and 6 mm from the overlap of the v. thalamostriata and plexus chorioideus or from the junction of the mentioned veins. *Results:* The median corridor width was 2 mm from the venous junction, 2.5-3 mm, and 4-4.5 at distances of 4 and 6 mm. A small nonconstant venous structure was observed in the dorsal part of the tuberculum thalami. After subtracting 1.3 mm (electrode diameter) from the width of the corridor, the reserve space at a distance of 2 mm is 1.2-1.8 mm and at distances of 4 and 6 mm from the junction is 2.7-3.2 mm. *Conclusion:* The narrow vascular corridor (especially in the anterior part of the ATN) places high demands on preoperative planning and implantation accuracy to maximize the effect of stimulation therapy while avoiding the risk of vascular conflict.

### Abstract

*Aim:* Stimulation of the anterior thalamic nucleus (ATN) is considered for patients with refractory epilepsy if there is no other surgical option. The target structure, the ATN, protrudes to the lateral brain ventricle as a thalamic tubercle, bordered by the thalamostriate vein laterally and the choroid plexus with the superior choroidal vein medially. The study aim was to analyze this vascular corridor for electrode implantation considering both surgical safety and possible association with stimulation outcomes. The best results are achieved when the anterior part of the ATN is stimulated. *Materials and methods:* The thalamic tubercle and its vascular borders were identified in dissection of both brain hemispheres of cadaveric specimens with intracranial vessel injections. The width of the vascular corridor was measured at distances of 2, 4, and 6 mm from the covering spot of the thalamostriate vein and choroid plexus or from the junction of these veins. *Results:* Six cadaveric specimens were measured. The median widths of the vascular corridor were 2.5-3 mm at the 2 mm, and 4-4.5 mm at the 4 mm, and 6 mm measures from the junction points, respectively. A small inconstant venous structure was observed in the dorsal part of the thalamic tubercle. After subtracting 1.3 mm (the diameter of a stimulation electrode) from the corridor width, the reserve space was 1.2-1.8 mm at the distance of 2 mm, and 2.7-3.2 mm at distances of 4 mm, and 6 mm from the junction, respectively. *Conclusions:* The narrow vascular corridor for electrode implantation (particularly in the anterior part of the thalamic tubercle) requires meticulous presurgical planning and precise implantation to maximize the effect of stimulation treatment while avoiding the risk of vascular conflict.

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The Editorial Board declares that the manuscript met the ICMJE "uniform requirements" for biomedical papers.

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Accepted for review: 29. 12. 2022

Accepted for : 2. 3. 2023

### Keywords

epilepsy - stereotactic techniques - noisy brain stimulation - anterior thalamic nucleus - vena thalamostriata

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## Home

In patients with pharmacoresistant epilepsy in whom resection of the epileptogenic lesion is not possible or epilepto-surgical resection does not lead to a decrease in seizure frequency, electrical stimulation of the left vagus nerve may be considered. This procedure gives more than 50% of patients a chance of at least a 50% reduction in epileptic seizure frequency [1]. In patients in whom vagal stimulation does not lead to a significant reduction in seizure severity and frequency, deep brain stimulation (DBS) is an option. Currently, the most commonly used target structure is the anterior thalamic nucleus (ATN). The ATN is a functional and anatomical part of Papez's limbic circuit with extensive connections to the sulcus, cingulum, corpora mammillaria and retrosplenial cortex. It is also a functional part of the hippocampal system. Thus, when the ATN is stimulated, there is functional modulation of large areas of the brain potentially responsible for the onset, propagation, and clinical symptomatology of an epileptic seizure [2,3].

Experience with lesional anterior thalamic nucleus surgery for epilepsy was reported in by Mullan et al [4]. The first reports on ATN stimulation in patients with far-macro-resistant epilepsy were published in 1985 [5].

tona et al and e.g. the report by Hodaie et al [6] reported positive results of ATN stimulation in terms of seizure reduction, a multicentre double-blind randomised SANTE (Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy) study became the impetus for wider use of ATN stimulation in patients with refractory epilepsy. The study included 110 patients who underwent bilateral implantation of stimulation electrodes into the ATN. In the initiated blinded phase of the study (3 months), stimulation was not activated in half of the patients. In these patients, the median decrease in the number of seizures was 14.5%. In the active stimulation group, the median reduction in seizure frequency 3 months after surgery was 40.4%. With a median reduction in seizure frequency of 56% 2 years after implantation [2]. Among the recent studies confirming the positive effect of ATN stimulation, a randomized double-blind study by Hermann et al [7] can be mentioned. In 2018, the Food and Drug Administration (FDA) approved ATN stimulation for the treatment of patients with far-macro-resistant epilepsy [8].

The anatomical relationships of the ATN differ fundamentally from other target structures of stereotactic surgery in some aspects (e.g., nucleus subthalamicus, nucleus ventralis intermedius of the thalamus, and globus pallidus internus). In contrast to the above structures, the ATN is located

subependymally in the lateral ventricle of the brain just posterior to the foramen Monroi. Its upper surface arches into the interior of the lateral (Fig. 1). When viewed from the interior of the lateral ventricle, the ATN corresponds to the tuberculum thalami, which is bordered on the lateral side by the v. thalamo-striata and on the medial side by the choroid with the draining vein (v. chorioidea superior). When implanting the stimulating electrode through the transventricular approach, the stimulating must pass through this corridor (Fig. 2). An alternative to the transventricular approach is the insertion of the electrode from the lateral approach under the

v. thalamostriata, however, even here the anatomical corridor is bordered by v. thalamostriata and the edge of the insula (sulcus circularis insulae) (Fig. 3). This trajectory is less used [8].

The aim of the presented experimental work was an anatomical analysis of the trajectory of stereotactic implantation of the stimulation electrode into the ATN in cadaveric models, focusing on the vascular relationships of the electrode trajectory, especially in the area of the described venous coronary sinus. These structures are essential for the safe and accurate implantation of the stimulation electrode into the ATN.

## File and methodology

For the study, preparations from the Anatomical Institute of the Faculty of Medicine in Brno were used, with the intracranial arteries and veins primarily used for educational courses focused on neurosurgical and otorhinolaryngological surgical approaches.

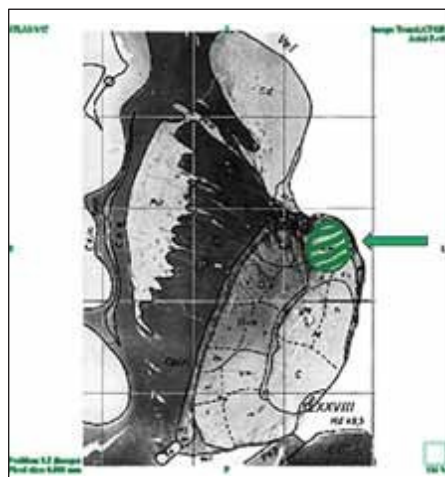


Fig. 1. The position of the nucleus anterior thalami (outlined in green) in relation to the structures of the ventricular system (taken the Schaltenbrand Bailey electronic atlas).

Fig. 1. The position of the anterior thalamic nucleus (green borders) and its relationship to the structures of the ventricular system (modified from the Schaltenbrand Bailey e-atlas).



Fig. 2. Coronal section through the brain at the level of the nucleus anterior thalami - the pedicle shows the course of the transventricular trajectory to the nucleus anterior thalami (blue arrow). The subependymal vein in the ceiling of the lateral ventricle (green arrow) can be seen close to the intended trajectory.

Fig. 2. Coronal section of the brain at the level of the anterior thalamic nucleus - the probe shows the transventricular trajectory to the nucleus anterior thalami (blue arrow). Subependymal vein located in the roof of the lateral ventricle in the proximity of the intended trajectory (green arrow).



Fig. 3. Lateral trajectory of the electrode to the nucleus anterior thalami - indicated by the pedicle. The blue arrows delineate the corridor for electrode insertion into the nucleus anterior thalami (indicated by the black box).

Fig. 3. Lateral trajectory of the anterior thalamic nucleus electrode - marked by the probe. Blue arrows delineate the lateral corridor for the anterior thalamic nucleus electrode (red dot) electrode.

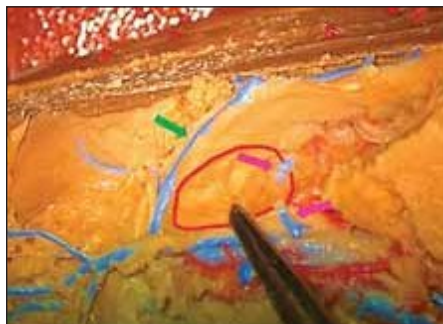


Fig. 4. Image of the tuberculum thalami from the lateral view (marked with tweezers and bordered by a red line). thorns of the vena thalamostriata structure (green arrow) and the venous structure located behind the tuberculum thalami, enters the vein draining the plexus chorioideus (purple arrows).

Fig. 4 Lateral view of the tuberculum thalami (marked with forceps and delineated in red). See the structure of the thalamostriatal vein (green arrow) and venous structure located behind the thalamic tuberculum entering the choroid plexus draining vein (violet arrows).

The first step in the preparation of the slides was dissection of the common carotid arteries, vertebral arteries and internal jugular veins. This was followed by cannulation and removal of blood clots and formalin residues by high volume water irrigation. Afterwards, injections of coloured silicone were manually administered - approximately 100 ml of silicone for arterial structures and 150 ml for venous trunks in one pre- parate. After injection, the slides were stored in 66% alcohol solution for approximately one day [9]. Although the quality of the slides was greatly affected by the achieved fixation of the brain tissue, identification of vascular structures was possible without significant difficulties.

Already in the study, horizontal incisions at the level of the lateral ventricular body were made in both hemispheres after preparation of the sulcus frontalis superior, sulcus cinguli and sulcus corporis callosi with evaluation of the quality of the vascular structures. In addition to the evaluation of the injection of the vascular structures and the quality of fixation of the brain tissue, this procedure allowed the identification of the foramen Monroi and the surrounding structures - tuberculum thalami, v. thalamostriata and plexus chorioideus with v. chorioidea superior. Vascular structures could be identified without any problems even on slides with imperfect fixation of brain tissue. For better identification of the structures and photographic documentation it was possible to use a dissecting microscope.

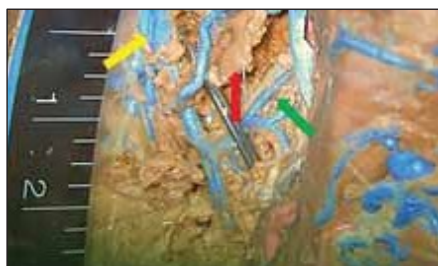


Fig. 5. Deep cerebral venous structures of the brain with a probe simulating the course of the stimulating electrode. The probe passes through the lateral ventricle and enters the tuberculum thalami between the choroid plexus (red arrow) and v. thalamostriata (green arrow). The relationship of the end of the inserted electrode is evident to v. cerebri interna (yellow arrow)

Fig. 5. Deep cerebral venous structures with the probe mimicking the course of implanted stimulation electrode. The probe passes through the lateral ventricle and enters the tuberculum thalami between the choroid plexus (red arrow) and thalamostriatal vein (green arrow). The relationship of the tip of the implanted electrode to the internal cerebral vein is readily seen (yellow arrow).

The basis of the study was the measurement of the width of the vascular corridor between the v. thalamostriata and the choroidal plexus with the v. chorioidea superior, which the stimulating electrode passes to the ATN. The corridor width was measured at distances of 2, 4, and 6 mm from the overlapping area of the choroidal plexus and v. thalamostriata, or, in the case of autolysed plexus, from the confluence of v. thalamostriata and v. chorioidea superior. Measurements were made using the attached scale and comparing the size of the structures with instruments of known diameter - e.g., a 1 diameter olive probe. Measurements could be made on six slides.

## Results

As shown in Fig. 2, the standard site of entry of the stimulating electrode is the gyrus frontalis superior, but depending on its width, the entry and the initial section of the trajectory electrode may extend close to the sulcus frontalis superior or pass through it. The fact that the nucleus anterior thalami is close to the midline and the electrode trajectory has a very acute angle with the midplane also implies the real possibility of the electrode passing through the sulcus cinguli or sulcus corporis callosi, as can also be seen in Figure 2.

After passing through the ceiling of the lateral cortex, the stimulating electrode passes through the



Fig. 6. Measurement of the width of the corridor between the v. thalamostriata (purple arrow) and the plexus chorioideus (v. chorioidea superior - red arrow) on the other side of the specimen based comparison of the width of the vascular corridor (estimated at 2.5-3 mm) with the diameter of probe (1.3 mm). Patterns of v. cerebri internae (yellow arrow).

Fig. 6. Measurements of the width of the corridor between the thalamostriatal vein (violet arrow) and the choroid plexus (superior choroidal vein - red arrow) on the second side of the specimen comparing the width of the vascular corridor (approximately 2.5-3 mm) with the probe diameter (1.3 mm). Internal cerebral veins are marked with a yellow arrow.

The lateral ventricle enters the tuberculum thalami between the choroidal plexus with the draining vein and the v. thalamostriata (Fig. 4). Although the fixation of the specimen shown in Fig. 5 is not as good as in the previous figure, thanks to the well-executed injection, it is possible to identify the vascular structures and to measure the width of the corridor for implantation of the electrode (here simulated with a probe). The measurements were made using the attached scale, but the findings can be confirmed by comparison with the preparation tool (Fig. 6). At a distance of 6 mm from the beginning of the corridor, a small venous structure, posteriorly penetrating the tuberculum thalami, could be clearly identified on four slides. This structure is also shown in Fig. 7 (here it enters the v. thalamostriata).

Measurements of the corridor width at defined distances were performed on a total of six slides (five slides bilaterally, on one slide only left-sided measurements were possible due to the disruption of the vascular structures on the right side). The results obtained are shown in Table 1.

Comparison of the measurement results showed an orthogonal asymmetry of the corridor width in four slides, which, however, did not exceed 1 mm. As an example of the influence of the width of the surgical corridor on the safety of implantation, we



**Fig. 7. Delineation of the vascular corridor for implantation of the electrode into the nucleus anterior thalami. The venous inflow to the v. thalamo-striatum is visible, just from the nucleus anterior thalami (marked by the probe). Partially covered structures of the plexus chorioideus**

Fig. 7. The borders of the vascular corridor for anterior thalamic electrode implantation. Venous tributary to the thalamostriatal vein from the anterior thalamic nucleus (marked with a probe). Partially preserved structures of the choroid plexus.

tuations with corridor widths of 2.5 mm and 3 mm (median of the corridor width at 2 mm from the beginning for the right and left side), 4 mm (median of the width at 4 mm from the beginning), and finally 4-4.5 mm (median of 6 mm from the beginning of the corridor). After subtracting 1.3 mm from the electrode diameter, a reserve of 0.85 mm for the left side and 0.6 mm for the right side remains at a distance of 2 mm and a reserve of 1.35 mm between the edge of the electrode and the edge of the v. thalamostriata and v. chorioidea superior (if the electrode were inserted exactly through the centre of the corridor). At a distance of 6 mm there is a margin of 1.35-1.6 mm.

**Discussion**

The aim of stereotactic planning of the target structure for implantation of the stimulating electrode is not only to place the electrode in the optimal area in terms of functional outcome, but also to minimize the risks of the procedure. We will evaluate the results of the experimental study from both perspectives.

Hemorrhagic complications of stereotactic procedures in deep brain structures are rare but potentially fatal. In the SANTE study, hemorrhagic complications were described in 4.5% of patients [2]. For comparison with other target structures, Binder et al reported a higher incidence of hemorrhagic complications during implantation of electrodes in the pallidum (6.7% of the total number of electrodes)

**Table 1. Quantitative measurements of the corridor for electrode implantation.**

Slide number and page	Corridor width in distance 6 mm (mm)	Corridor width in distance 2 mm 4 mm (mm)	Corridor width in Corridor width in Corridor width in (or level dorsal veins) (mm)
1 on the right	2	3	3
1 left	3	4	4
2 right	2,5	4	4
2 left	2	3	3
3 right	3	4	5
3 left	3	4	6
4 right	3	4	5
4 left	2	4	6
5 left	3	4	5
6 right	2	5	3
6 left	3	4	3
median overall	3	4	4
median for the right side	2,5	4	4
median for the left side	3	4	4,5

than implantation of electrodes into the subthalamic nucleus (2.5% of the total number of electrodes) [10]. To illustrate the possible causes of haemorrhagic complications during implantation of electrodes into the anterior thalamic nucleus, it is necessary to summarize the anatomical characteristics of the stereotactic trajectory (Fig. 2). An important factor is the proximity of the target structure to the midline. Standard coordinates of the ATN in relation to the inter-commissural line are reported to be in the range of 0-2 mm anterior to the midline, 10-12 mm above the inter-missural line, and most importantly only 5.5 mm lateral to the midline. In comparison, the lateral coordinate of the target in the globus pallidus internus ranges from 19-21 mm. As can be seen from this fact and the relationship of the target structure to the v. thalamostriata located at its lateral edge, it is necessary to place the trepanaci for the insertion of the intracerebral electrode closer to the midline than, for example, in the case of the v. thalamostriata. Although the electrode entry is usually located in the gyrus frontalis superior, depending on the anatomical conditions, the trajectory may also extend into the sulcus frontalis superior, which increases the risk of torsion [11]. Further along the trajectory, the electrode reaches close to the lateral margin of the sulcus cinguli and sulcus corporis callosi with the possibility of injury to the branches of the a. pericallosa and a. callosomarginalis.

Although modern stereotactic planning techniques allow detailed analysis of the planned trajectory in relation to vascular structures, Nowinsky et al state that the planning MR scans used (1.5 or especially 3T) may not be sufficient in terms of imaging surgically important vascular structures. Their proposed 3D stereotactic cerebrovascular atlas (derived from 3T and 7T MR scans) captures more than 900 vessels with an assigned name and specified diameter located near standard stereotactic trajectories. During standard implantation of a stimulation electrode into the nucleus subthalamicus or globus pallidus internus via the gyrus frontalis medius, several arterial structures must be considered - the anteromedial branch of the arteria cerebri anterior, the prefrontal branch of the same artery and the arterial supply of the sulcus precentralis arising from the a. cerebri media with diameters ranging from 0.4 to 0.6 mm. All of the above-mentioned arteries must also be narrowed when approached by the gyrus frontalis superior. Relevant venous trunks include the prefrontal, anterior caudate and medullary veins (diameter range 0.1- 2.3 mm) and, for implantation of the electrode in the ATN, additionally the v. thalamostriata and v. chorioidea superior, but also the nonconstant venous structure bordering the tuberculum thalami dorsally identified in the study [12].

The risks associated with transventricular electrode conduction are discussed in the paper by Elias et al, according to which asymptomatic intra-ventricular bleeding during passage of the electrode through the cerebral ventricle was demonstrated in 5% of patients [11]. In terms of vascular structures associated with the risk of intra-ventricular haemorrhage when the electrode passes through the ventricle, the subependymal veins are important. However, the corridor between the v. thalamostriata and the choroid plexus with the v. chorioidea superior remains the most important vascular problem when implanting an electrode into the ATN. As our results show, this vascular corridor is narrowest in the anterior part. Thus, if we consider only the risk of vascular injury, a slightly wider posterior part of the vascular corridor may be safer for electrode implantation. However, other factors related to the functional anatomy of the anterior thalamic nucleus must also be taken into account.

Based on 3T MR measurements, the mean length of the ATN in the anteroposterior axis is 10 mm, the width is approximately 5.5 mm and the height is 4.5 mm. However, the apparently large anterior thalamic nucleus consists of three parts (anteromedial, anteroventral and anterodorsal) [13]. The connections with the temporal lobe are most important for the function of the anteroventral nucleus, and the anteromedial nucleus is extensively involved in the orbitofrontal circuit. The anterodorsal nucleus in the posterior part of the nucleus anterior thalami is part of another functional circuit involving the lateral mammillary nucleus and is thought to be responsible for memory and navigation in the primum. Given these functional relationships, a greater effect of stimulation on partial seizures can be expected when the anteroventral (connections with the temporal lobe) or anteromedial nucleus (orbitofrontal cortex) is stimulated [2]. Consistent with this reasoning, Lehtimäki et al, in an analysis of the position of individual ATN electrode contacts, demonstrated that good results in terms of seizure control are obtained when contacts located in the anterior part of the ATN (corresponding to the anteroventral and anteromedial nuclei) are stimulated [14]. Wu et al in non-responders demonstrated a tendency to locate stimulated contacts in the posterior and lateral part of the ATN. Another finding is the smaller size of the ATN in non-responders [15]. A counter-current effect was not observed in the stimulation of the posterior and inferior part of the nucleus even in the animal model [16]. Thus, the above results support the necessity of implanting an active contact in the anteroventral and

anteromedial region of the thalamic nucleus, i.e., the anterior part of the nucleus, by way of the anterior vascular co

ridor [17]. The right asymmetry of the ATN position is also an important factor. According to Lehtimäki et al, in most patients, the right ATN was more anteriorly located compared to the left side [14]. We did not address the issue of the rightward symmetry of the target structures' position, but measurements in four specimens showed a rightward asymmetry of the corridor width, which, however, did not exceed one mm.

Although this issue is only marginally mentioned in the anatomical study, we consider it appropriate to provide some indications of alternative trajectories for the implantation of the DBS electrode into the ATN from the lateral approach (Fig. 3). In all patients enrolled in the SANTE study, the electrodes were implanted transventricularly [2]. In a retrospective analysis of the course of the six electrodes inserted into the ATN from the lateral approach, Lehtimäki et al found that no contact could be said to be uniquely located in the ATN, let alone in the anteromedial or anteroventral part of the nucleus [14].

More optimistic data are provided by the MORE study, the aim of which was to compare the trans-ventricular and lateral (extraventricular) approaches in terms of stimulus contact localization. The study included 73 patients and the lateral approach was used for 53% of electrode implantations. At least one stimulating electrode contact was located in the ATN in 90% of the electrodes implanted transventricularly and in 71% of the electrodes implanted from the lateral approach. In 84% of patients with electrodes implanted transventricularly, both electrodes reached the ATN, which was true for only 58% of patients with electrodes implanted from the paraventricular approach [18].

Regarding the limitations of the study, apart from the infinite quality of the fixation (which did not pose a problem for the identification of venous structures), it is necessary to mention the assumption that the age of the donors is higher than the age of the patients in whom the electrodes are implanted in the ATN area (according to the data from the SANTE study  $36.1 \pm 11.2$  years) [2]. The age-related decrease in ATN volume mainly affects the medial and anterior parts of this structure, which can be explained by atrophy of the frontal and temporal lobes [14,19].

## Conclusion

The use of the transventricular approach for implantation of electrodes into the nucleus anterior thalami in patients with otherwise uncontrollable pharmacoresistant epilepsy is essential

the question of the passage of the stimulating electrode through the vascular corridor bordering the tuberculum thalami. Its outer border is the v. thalamostriata and medially it is bounded by the choroidal plexus and the draining vein of the v. chorioidea superior. The anatomical study also showed non-constant small venous structures bordering the tuberculum thalami dorsally. The measured width of this corridor ranges from 2-3 mm in the anterior part, 3-5 mm in the middle part and reaches 3-6 mm in the posterior part. Since the functionally optimal area for electrode implantation is located in the anterior part of this corridor, after reading the electrode diameter, the margin ranges from 0.6-0.8 mm for a distance of 2 mm from the beginning of the corridor and reaches 1.3 mm for a distance of 4 mm from the beginning of the corridor, which places high demands on the accuracy of stereotactic systems and trajectory planning

### Ethical aspects

The study on human subjects described in the manuscript was performed in accordance with the ethical standards of the Ethics Committee of the St. Anne's Hospital in Brno responsible for conducting clinical trials and the Declaration of Helsinki of 1975, revised in 2000. All specimens were obtained from body donors to the Anatomical Institute who had already given their consent to be used for anatomical studies during their lifetime. For this, ethics committee approval was not required.

### Grant support

Supported by the PRESEnCE project - AZV-NV- 19-04 - 00343. All rights under intellectual property protection regulations are reserved

### Declaration of Conflict of Interest

The authors declare that they have no conflict of interest in relation to the subject of the work

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