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Collapsibility of the internal jugular veins in the lateral decubitus body position: A potential protective role of the cerebral venous outflow against neurodegeneration

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ABSTRACT

Recent research has revealed that patients with neurodegenerative disease sleep longer in the supine position, while healthy controls prefer sleeping in the lateral decubitus position. Thus, sleeping in the lateral position seems to be protective against neurodegeneration. It has also been suggested that a protective role of this body position could be associated with better cerebral venous drainage in this body position, which results in more active glymphatic system of the brain (the system responsible for clearance of the cerebral tissue from waste products, e.g. amyloid-β). Since no published evidence exists regarding venous outflow from the cranial cavity in the lateral decubitus position, we performed a pilot sonographic study of the internal jugular veins in 3 young healthy volunteers and 2 patients presenting with abnormal jugular valves. In all healthy volunteers both internal jugular veins were opened in the supine position and collapsed in the sitting one. In the right lateral decubitus position the right internal jugular vein was opened, while the left one was partially collapsed; and—vice versa—in the left lateral decubitus position the right internal jugular vein was partially collapsed and the left one opened. In patients with abnormal jugular valves both internal jugular veins were opened in both lateral decubitus body positions. We hypothesize that in the lateral decubitus body position, because of decreased flow resistance in the extracranial veins, cerebral venous outflow is optimal, which in turn optimizes the activity of the glymphatic system. Therefore, people intuitively prefer this body position during sleep, while other positions are associated with a higher risk of neurodegenerative disorders. Yet, it should be emphasized that our results need to be interpreted with caution, since only a few individuals have been assessed and this discovery should be confirmed in more patients and healthy controls, and by precise quantitative measurements.

Introduction

Although it is suspected that pathomechanism of neurodegenerative diseases may be associated with the toxicity of proteins retained in the cerebral parenchyma, details of this process remain unclear [1–3]. Recently an intriguing paper, which may shed new light at this problem, has been published. The authors of this study—basing on data coming from three multicentre studies—have found that patients with neurodegenerative disease, in comparison with their age- and sex-matched controls, were more likely to sleep in the supine position. The controls, on the contrary, slept longer in the lateral decubitus body position [4]. Of note, since only 45 subjects were investigated, this report should be seen as preliminary and needs confirmation by other, prospectively designed studies. Yet, although these observation should be interpreted with caution, nonethless they may become a fertile subject of inquiry. Although it was possible that a longer sleep in the supine position resulted from neurodegeneration, the authors hypothesized that rather an opposite relationship played a role, namely that sleep in the lateral position was somehow protective against neurodegeneration. Such a scenario, they suggested, would be in line with the results of animal experimental study published by Lee et al. [5]. In this study mice sleeping in the lateral position exhibited a better functioning glymphatic system and had a faster clearance of their brains from amyloid-β. Also other parameters of the glymphatic system were better if rodents (rats and mice were used in experiments described in this paper) slept in the lateral decubitus position [5]. Thus, it seemed that sleep in the lateral body position may be preventive against accumulation of deposits of pathological proteins (such as amyloid-β, but

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potentially also tau or α- and β-synuclein) through an enhanced efficacy of the clearance of cerebral tissue by the glymphatic system in this particular positioning of the head. If it actually were true, this phenomenon could be used for the prophylaxis and treatment of Alzheimer's and other neurodegenerative diseases, and should also be taken into account while designing future clinical and experimental studies on neurodegeneration. In this paper we present current knowledge and conjectures regarding possible associations of sleep in the lateral decubitus position with the activity of glymphatic system. We also present a roadmap of suggested future research on this topic and our preliminary findings on the collapsibility of the internal jugular veins in this particular body position, a phenomenon that has not been previously reported and which may play a role in the regulation of activity of the glymphatic system during sleep.

How the glymphatic system is activated during sleep

Currently, it is not precisely known which mechanism actually activates the aquaporin-4 water channels—the main components of the glymphatic system—in the asleep brain [6–11]. One of possible explanations is that noradrenergic system of the brain directly affects astrocytes [12,13]. Most of researchers suggest that an increased pulsatility of the cerebral blood vessels during sleep activates the glymphatic system through pumping of the cerebrospinal fluid alongside small cerebral arteries [6,7]. Even if it actually is the case, what is responsible for this enhanced pulsatility, remains to be unequivocally demonstrated. Probably a direct transmission of the pulsatility from large arteries plays a minor role. Most likely, this pulsatility is primarily regulated locally, by the cerebral norepinephine system through the specialized neurons located in the locus coeruleus of the brainstem, and such a mechanism has been indirectly confirmed by animal studies [8–11]. Still, probably other mechanisms play here an additional role, since the influence of body position during sleep [5] could hardly be explained by noradrenergic signaling. Small cerebral veins could be one of such an alternative target. Of note, although it is known that water molecules primarily leave the intercellular space through the aquaporin-4 channels expressed by astrocytes at the venous side of the perivascular space [3,6,7], details regarding venous side of the glymphatic system are still enigmatic. And even less is known about potential influence of an impaired venous drainage of the brain on the activity of the glymphatic system, although a higher risk of neurodegeneration in the settings of impaired venous outflow from the brain, which is seen in patients presenting with obstructive sleep apnea [14] may suggest such a link. Some authors have also suggested that jugular reflux, which negatively affects cerebral venous drainage, may be associated with neurodegeneration [15–17] or that such a reflux may impair the function of the glymphatic system [18].

Why sleep in the lateral position is associated with more active glymphatic system and why the right lateral position is preferred by humans

In this paper we have already described that it is generally assumed that activity of the glymphatic system is primarily regulated by noradrenergic system of the brain. Yet, the study by Lee at al. [5] has not explained why the noradrenergic stimulation should be increased during sleep in the lateral decubitus position. One of possible explanations would be that noradrenergic neurons are stimulated by the vestibular nuclei that receive inputs from the semicircular canals, utricle, and saccule of the labyrinth. Of as yet, such anatomical connections have not been revealed, but there is one important phenomenon that indicates that such a stimulation is very unlikely. It is well known that humans prefer to sleep in the lateral position (albeit not all published studies confirm this phenomenon), but interestingly – mostly on the right side [19,20]. Why this particular body position is the favored one, remains elusive [11]. But if a stimulation coming from the vestibular nuclei were playing a role, a lateralized sleep pattern favoring the right side should not be expected. In the past, several mechanisms of the preference of the right decubitus position during sleep have been proposed but all of them seem rather unconvincing (including an idea that heart beating is better felt while lying on the left side and therefore people dislike sleeping in this position) [21,22]. It is known that—in comparison with the right decubitus and supine body positions—the left lateral decubitus position is associated with a lower heart rate [23,24], but whether this phenomenon results from decreased activity of the autonomic sympathetic nervous system, or it is simply a physiological adaptation of the heart to the topographic locations of particular organs within the chest in different body positions, has not been unequivocally explained. Nonetheless, these findings are unlikely to be linked to the activity of the glymphatic system. Moreover, heart rate does not explain why people sleep mostly in the right lateral decubitus position. Similarly, suggested links with the patency of the upper respiratory tract in different body position, except for patients with severe respiratory disease, are unconvincing. At the moment only a few papers—not associated with respiratory disease—dealing with this particular body position during sleep have been published. A study assessing sleep behavior in low-pressure glaucoma patients has revealed that those sleeping longer in the right lateral decubitus position had more severe disease; interestingly, predominantly in the left eye [20]. Thus, a lateral decubitus body position is not always beneficial.

Despite this relative lack of evidence, most likely humans (and also many mammals) prefer to sleep in the lateral decubitus position, because in this body position the glymphatic system is more active and the clearance of cerebral tissue from waste products—which seems to be one of the most important roles of sleep—is better carried out in this particular body position. Furthermore, it seems that in humans, for some reasons, the right lateral position is preferred and it is possible that this body position is better than the left one regarding the function of the glymphatic system. Therefore people prefer to sleep on the right side. An anatomical lateralization of cerebral structures would favor this hypothesis - and indeed, such an asymmetry is well known. Namely, it is the anatomy of intra- and extracranial veins draining the brain, which in humans are usually lateralized and—importantly—typically dominant on the right side [25].

How does blood flow out of the brain

In order to better understand possible links between the venous and glymphatic systems, a brief description of anatomical and physiological aspects of venous outflow from the cranial cavity should be presented. Although a majority of principal parts of the brain in mammals—including also humans—are paired, main venous channels are single and located in the midline [26,27]. Main venous channels draining the brain comprise the superior sagittal sinus, the inferior sagittal sinus, the great cerebral vein, the straight sinus and the occipital sinus. The superior sagittal sinus is the principal blood vessel draining both cerebral hemispheres (a part of the venous drainage from the cerebral cortex empties also into the cavernous and transverse sinuses). Blood from deep structures of the brain (the basal ganglia, the thalami and a majority of cerebral white matter) drains into the deep venous system of the brain. Main veins of this system comprise the internal cerebral veins and the basal veins of Rosenthal that finally drain into the great cerebral vein, which—together with the inferior sagittal sinus—empties into the straight sinus. A dilated posterior termination of the superior sagittal sinus connects with the straight, transverse and occipital sinuses to form the confluence of sinuses. In humans anatomy of this confluence is highly variable. A symmetric confluence of sinuses, joining all of the above-mentioned sinuses, is rarely encountered (in about 15% of people). Typically, the right transverse sinus is the main continuation of the superior sagittal sinus, with large asymmetry of the connections with other cerebral sinuses. Quite often deep structures of the brain, through the great cerebral vein and the straight sinus, drain exclusively into one of the transverse sinuses, typically the non-dominant one. From the confluence of sinuses both transverse sinuses run laterally. A direct continuation of each transverse sinus is the sigmoid sinus. The sigmoid sinus then joins with the inferior petrosal sinus and forms the bulb of the internal jugular vein. Because of a typical asymmetry of the confluence of sinuses, the internal jugular veins transport unequal volumes of blood; a dominant right internal jugular vein is more prevalent [25].

Flow patterns depending on body position should also be taken into account. In humans blood flows out of the cranial cavity through two alternative pathways: through the internal jugular veins or through the paravertebral route, comprising the spinal epidural plexus and the vertebral veins. In the supine or prone body positions blood primarily flows through the internal jugular veins. However, when the head is elevated, a substantial amount of blood flows out via the paravertebral route [28–30] (this is a dominant outflow route in mice and rats, which should be considered when interpreting the results of animal experiments), which is connected to the intracranial veins through the spinal epidural plexus and the suboccipital cavernous sinus. This route primarily consists of the vertebral veins that drain into the subclavian veins. A minority of blood, through the spinal epidural plexus, can also drain into the azygos vein system [25]. There are also small connections between intracranial veins and the territory of the external jugular vein, but this pathway is rather negligible in humans. In some mammals, like rodents, this outflow route is very important; it primarily comprises the postglenoid vein that typically is not seen in adult humans [26,31–33]. These two outflow routes, the jugular and the paravertebral, are very well interconnected by many venous channels, mostly in the area of the jugular bulb [34]. Different outflow patterns from the cranial cavity depend on body position, but are not actively regulated by vascular musculature. They result from physical effects, primarily from collapsibility of the internal jugular veins [35,36]. Although in humans the cross-sectional area of the internal jugular veins is comparable to the total cross-sectional areas of the vertebral veins and the spinal epidural venous plexus, in the supine body position—when the internal jugular veins are opened—flow resistance in the paravertebral route, which consists of a network of small veins, is much higher than in the internal jugular veins. Consequently, in this body position a majority of blood flows out through the internal jugular veins. On the contrary, in an upright body position the internal jugular veins partially collapse, which in turn significantly increases flow resistance. The vertebral veins and other veins located deep inside the neck are supported by adjacent tissues. Their collapse in the upright position is insignificant and therefore in standing or sitting humans a substantial amount of blood is shifted towards the paravertebral route [29,30,35,36]. In addition, it should be remembered that cerebral venous outflow depends also on respiratory movements and the pressure inside the thoracic and abdominal cavities. These factors can be of particular importance in patients presenting with respiratory failure or obstructive sleep apnea. On the other hand, slightly increased central venous pressure, which is seen in the prone body position, probably facilitates cerebral venous outflow [37,38].

Interestingly, very little is known how does blood flow out of the brain in the lateral decubitus position. Typically, sonographic or venographic evaluation of the internal jugular and vertebral veins is performed in the supine position. For the diagnosing of the so-called chronic cerebrospinal venous insufficiency it is also recommended to study these veins in an upright (usually sitting) position [39,40]. But there is virtually no published evidence how do the internal jugular veins behave in the lateral decubitus position. There are some reports on sonographic assessment of these veins in the supine or prone positions with patient's head rotated [41–44]. But in this particular position of the head veins of the neck can be squeezed by adjacent neck muscles. Moreover, these observations would not be very helpful for our reasoning, since a supine position with head rotated to one side is not the one preferred during sleep.

Preliminary findings on the spontaneous collapse of the internal jugular veins in the lateral decubitus position

In the lateral decubitus position one internal jugular vein is situated slightly above the level of the right atrium of the heart, while the opposite vein is located slightly below this level. Since pressure differences in these veins in this particular body position resulting from hydrostatic effects should not exceed a few cmH_2O, it is difficult to predict theoretically whether they would collapse or not. Since no published evidence exists regarding this issue, we performed a pilot sonographic study of these veins in 3 young healthy volunteers (medical students). We performed this examination in four different positions: the supine, sitting, right lateral decubitus and left lateral decubitus. In all healthy controls, in order to exclude abnormalities suggestive of the so-called chronic venous insufficiency [35,39,40] and possible associated hemodynamic effects, we also examined jugular valves (valves located just above the junction of the internal jugular vein with the brachiocephalic vein). We interpreted these valves as abnormal if they presented with malformed and/or immobile (revealed by M-mode imaging) valve leaflets, or there was flow arrest, reflux or significantly increased blood flow velocity at the level of such a valve [40]. In addition, we performed sonographic assessment of the internal jugular veins in 2 patients who were referred to the outpatient clinic for screening of carotid arteries and during this examination were diagnosed with abnormal jugular valves (using the above-described criteria). Although typical sonographic protocol for carotid artery screening recommends an examination in the supine position (slight head rotation is also allowed), for the purpose of this pilot study we also assessed the internal jugular veins in the lateral decubitus position.

Our pilot study has revealed that in all healthy volunteers jugular valves were normal on both sides. Regarding diameters of the veins - both internal jugular veins were opened in the supine position (Figs. 1C, 2C) and collapsed in the sitting one (Fig. 1D, 2D). In the right lateral decubitus position the right internal jugular vein was opened (Fig. 1A), while the left one partially collapsed (Fig. 2A); and—vice versa—in the left lateral decubitus position the right internal jugular vein was partially collapsed (Fig. 1B) and the left one opened (Fig. 2B). Interestingly, in the lateral body position the vein located lower, for example the right internal jugular vein in the right lateral decubitus position, was slightly wider in comparison with the cross-sectional area of this vein in the supine position (Figs. 1A, 2B). In patients with abnormal jugular valves both internal jugular veins were opened in both lateral decubitus body positions (an example is shown in Fig. 3).

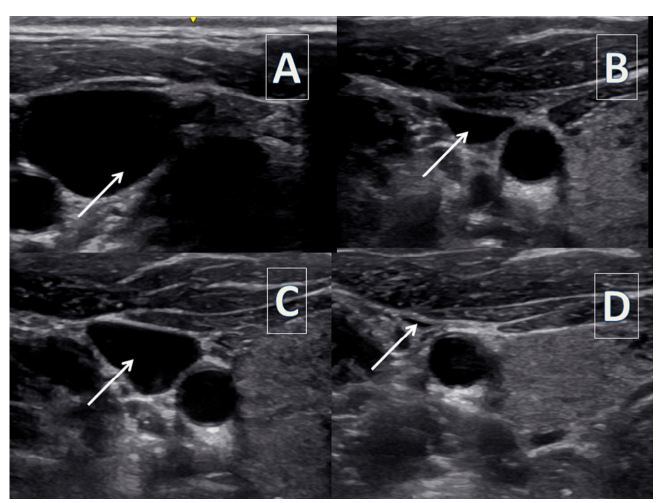

Fig. 1. Right internal jugular vein (arrow) in healthy control; A – right lateral decubitus position, B – left lateral decubitus position, C – supine position, D – sitting position.

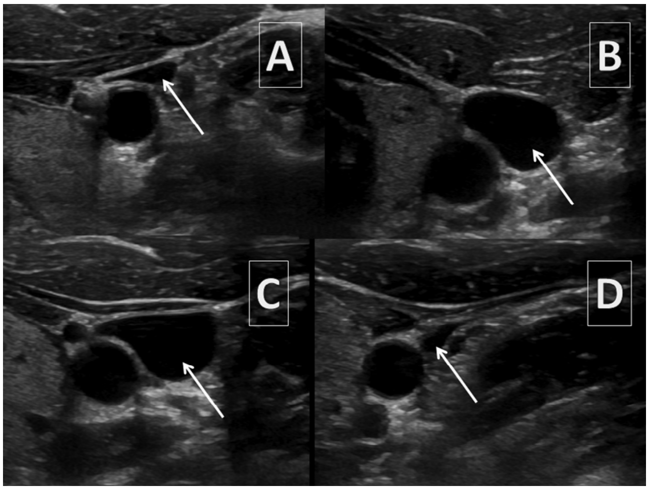

Fig. 2. Left internal jugular vein (arrow) in healthy control; A – right lateral decubitus position, B – left lateral decubitus position, C – supine position, D – sitting position.

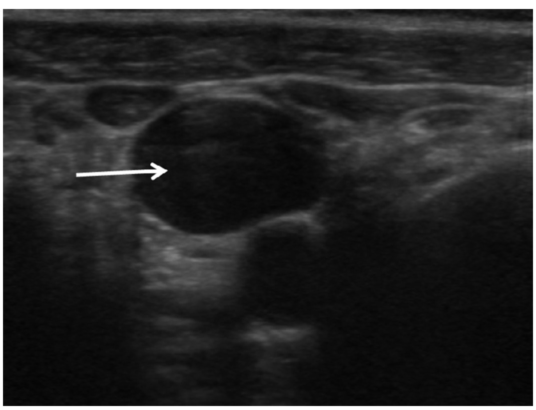

Fig. 3. Left internal jugular vein (arrow) in a patient in the right lateral decubitus position, the vein is fully opened, this patient presented with abnormal jugular valves of both internal jugular veins; in healthy controls vein located in a lateral position above the heart level was collapsed (Figs. 1B and 2A).

Suggested future research on cerebral venous outflow in the lateral decubitus position

In the context of possible link between extracranial veins with the activity of glymphatic system, results of our pilot study in healthy individuals seem counterintuitive. Yet, it should be emphasized that our results need to be interpreted with caution, since only a few individuals have been assessed. Undoubtedly, more patients and healthy controls should be examined, but our findings are probably the first ones regarding collapsibility of the internal jugular veins in the lateral decubitus body position and therefore may provide a useful framework for future research. One might assume that if an activity of the glymphatic system were dependent on good cerebral venous drainage through the internal jugular veins, both of these veins should be fully opened. But physical aspects of venous return from the cranial cavity could be more complex than expected. A flow through only one of these veins could be not worse than flow through two of them. According to the Hagen-Poiseuille's law, flow resistance in blood vessels, in addition to their cross-sectional area, depends also on viscosity of the fluid. And in the case of blood this viscosity is highly affected by velocity. Blood is a non-Newtonian, shear-thinning fluid. At low shear its viscosity increases by a factor of 4–5. Therefore, it cannot be excluded that— because of these viscosity-associated effects—flow resistance in one internal jugular veins (especially the right one, which is shorter that the left internal jugular vein together with the left brachiocephalic vein) is lower than a total flow resistance in two internal jugular veins. Another reason for this hypothetically lower flow resistance would be a dilatation—due to hydrostatic effect—of the vein located below the heart level. Our preliminary findings suggest that actually such a slight dilatation can be seen. Yet, this discovery should be confirmed in more individuals and by precise measurements. On the other hand, a lack of collapse of the internal jugular vein located above the heart level in patients presenting with malformed valves was suggestive of a relative hypertension in such a vein resulting from compromised outflow at the level of malformed valve.

If our preliminary findings on the collapsibility of the internal jugular veins in the lateral decubitus body position—in healthy people and patients presenting with abnormal jugular valves—will be confirmed in a larger cohort of patients and controls, this phenomenon would shed new light at potential associations of this body position with the activity of glymphatic system. We hypothesize that in the lateral decubitus body position, because of decreased flow resistance in the extracranial veins, cerebral venous outflow is optimal, which in turn optimizes activity of the glymphatic system. Therefore, people intuitively prefer this body position during sleep, while other positions are associated with a higher risk of neurodegenerative disorders because of an impaired glymphatic clearance. If it actually were the case that cerebral venous drainage is optimal with only one of the internal jugular veins fully opened, it should be expected that right lateral decubitus body position during sleep would be preferred, since typically a majority of blood is drained through the right internal jugular vein (except for individuals presenting with dominant left internal jugular vein).

Yet, in order to further elucidate these conjectures, quantitative studies should be performed, with measurements of flow velocities and flow volumes in the internal jugular veins and vertebral veins in different body positions. Such studies—optimally—should be performed using sonographic and magnetic resonance methods. Also, anatomical pattern of the intracranial cerebral venous drainage should also be taken into account. Consequently, we would suggest checking whether a preferred body position during sleep is associated with an anatomical pattern of the cerebral sinuses. It might be expected that people with a dominant cerebral drainage through the left transverse and sigmoid sinuses would prefer sleeping in the left lateral decubitus body position, thus differently than a majority of people with dominant right-sided venous drainage. For the purpose of such a research standard sleep recording should be used, together with MR images of head utilizing sequences depicting major cerebral sinuses. Perhaps, source data of the studies that have evaluated sleep pattern in patients presenting with neurodegeneration, already comprise such MR images and therefore it would be relatively easy to conduct retrospectively such a survey. Also, future research aimed at confirmation of results published by Levendowski et al. [4] should take into account lateralization of the parameters studied (right vs. left lateral decubitus position, right vs. left dominant internal jugular vein, etc.) In addition, an influence of abnormalities localized in the extracranial portion of the internal jugular veins in the context of sleep and neurodegeneration should be studied. Small-sample studies published by Beggs et al. has revealed swelling of brain tissues in Alzheimer and mild cognitive impairment patients presenting with jugular reflux [45]. Another pilot study by this team demonstrated more frequent white matter abnormalities in Alzheimer patients with associated jugular reflux [17]. Currently, it remains elusive which mechanisms are actually responsible for these phenomena. Perhaps future research on this topic should elucidate whether an impaired glymphatic function in the settings of abnormal cerebral venous drainage resulting from jugular reflux plays here a role.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://

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