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COMMENTARY

Does the brain have mechanical compliance?

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The terms "intracranial compliance" and "brain compliance" are often used interchangeably in the cerebrospinal fluid (CSF) literature [1, 2]. It is therefore time to clarify what intracranial compliance is and whether brains have compliance. The impetus for this commentary is a sentence I read while reviewing a manuscript; "Intracranial compliance is the ability of the brain to adapt to changes in intracranial volume while maintaining intracranial pressure". I had to read it twice because compliance has a lot to do with changes in volume and pressure but nothing to do with the ability of the brain to adapt to these changes. The notion behind "brain compliance" is likely related to the perception that the brain is "soft" and therefore it can accommodate a change in volume. The brain is not "soft" in the same way that water is not soft as both are incompressible within the physiological range of pressure changes. The brain material is viscoelastic, it is pliable, it can change its shape upon application of force, it is deformable and its resistance to deformation is termed stiffness [3]. The stiffness of the brain can actually be measured without touching it using MR elastography (MRE) [4] by imaging the propagation of shear waves through the brain caused by mechanical vibrations. Brain MRE is a maturing technique that is being used to map the stiffness of tissues throughout the brain in the healthy and disease states [5].

In contrast to stiffness, which is a property of material (in our case, brain tissues), compliance is the property of a compartment with well-defined boundaries (in our case, the cranium). The compliance of a compartment is defined by the change in its volume with respect to a change in the inside pressure. Intracranial compliance (ICC) is therefore the slope of the volume-pressure relationship (dV/dP) at a given intracranial volume (ICV) and intracranial pressure (ICP). The actual ICC is derived by the ratio of the volume and pressure changes, i.e., ICC = ΔICV/ΔICP. Therefore, the unit of compliance is volume divided by pressure. Anything with a different unit, such as phase delays between blood and CSF flow waveforms, which had been used as an estimate of ICC because the phase delay can be affected by the system compliance [6–8], is not compliance.

ICC is not constant; it changes with a change in volume and pressure and it rapidly decreases with increase in ICV. This is due to the fact that ICP is an exponential function of ICV [9]. Because of this exponential relationship, intracranial elastance, which is the inverse of compliance, i.e., dP/dV, is also an exponential function of ICV, as shown in Eq. 1,

$$ICE = \frac{1}{ICC} = E_1 * P_1 * e^{E_1 * ICV} \quad (1)$$

where ICE is intracranial elastance, E_1 is elastance coefficient constant of the bounding material, and P_1 is the baseline pressure. The nonlinear dependency of ICC on ICV explains why it is more difficult to clinically manage ICU patients once their ICP is elevated. In short, large ICC enables accommodation of a large volume without a large increase in ICP. When ICC is small, the same increase in ICV will cause a larger increase in ICP.

Another misconception that hinders the understanding of the concept of ICC is the notion that the volume of the intracranial compartment is constant because the skull is rigid. The well-known Monro–Kellie doctrine [10], which states that the sum of the volumes of the brain, blood and CSF is constant, further contributed to this misconception. I wish the phrase "nearly constant" would have been used instead, but back in the mid-1800s this was an important advancement in the understanding of the CSF physiology. Whereas the volume of the cranium is on the order of a 1.5 L, the maximal cardiac-related change in ICV is on the order of a milliliter (~0.1% of ICV). Therefore, in steady state, the ICV is "nearly" constant. The ability of the cranium to accommodate a small change in volume provides the cranial vault with its mechanical compliance. The cardiac-related pulsation of the ICP is the evidence for the small change in

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the ICV during the cardiac-cycle. So, where does the ICV change come from?

The boundary of the cranial compartment, the dura matter, has room to expand near the foramina where it is not confined by the skull. Additionally, the skull is not absolutely rigid. For example, a portion of the temporal bones have some mobility. An ultrasound-based method to noninvasively measure ICP, developed by NASA, demonstrated changes in the distance between the temporal bones, which then were used to estimate changes in ICV [11]. However, ICP cannot be estimated without knowing the ICC. Marmarou et al. were the first to establish the mono-exponential relationship between ICP and ICV from measurements of ICC [9]. They infused a known volume of saline into the cranium and measured the resulted increase in pressure, the ratio of the injected volume and the increase in ICP estimated the ICC [9]. Since then several infusion-based methods with different infusion strategies were proposed [12, 13]. However, infusion methods have several principle limitations. First, a relatively large volume of fluid, on the order of several milliliters, is infused to overwhelm the natural pulsation of the ICP caused by the small cardiac changes in the ICV of less than a milliliter, thereby, the ICC state is altered. Second, the injection occurs over a period of several cardiac cycles, therefore other processes that may interfere with the volume change, such as CSF absorption, may occur. Another critical limitation is the fact that some of the infused fluid goes to the spinal canal, thus the exact change in the ICV is unknown. So, is there another way to measure ICV change and ICC?

The MRI Era of CSF dynamics

The development of velocity-encoding MRI in the late 1980s brought a dramatic progress to the field of CSF dynamics. Dynamic velocity-encoded (venc) imaging with cine phase-contrast provided, for the first time, the ability to measure volumetric flow rates, noninvasively [14]. Shortly after the invention of the cine phase-contrast technique, it was applied to measure blood and CSF flows to, from, and between the different compartments of the craniospinal system [15, 16]. Prior to the MRI era, invasive blood and CSF pressure recordings were the primary tool for the investigation of the CSF dynamics. Velocity imaging with MRI provided the means by which the ICV change during the cardiac-cycle can be measured [17]. Fortunately, the blood and CSF are incompressible, and the anatomy of the inlets and outlets of the cranium is favorable for the measurement of the volumes of fluids that enter and leave the cranium with only two scans, a high-venc scan for the arterial inflow and venous outflow, and a low-venc scan for the CSF flow [17]. Figure 1a provide a representation of the inlets and outlets of the intracranial compartment used in the derivation of the ICV change during the cardiac cycle.

MRI measurement of the intracranial volume change and compliance

Measurement of the small changes in ICV during the cardiac-cycle is challenging as a small value is derived by subtraction of large volumes of fluids that enter and leave the cranium. Therefore, great care is required in performing the measurement. There are three critical details that affect the reliability of the measurement: (1) the location of the imaging planes for the blood and CSF flows, (2) the cardiac phases at which the blood and the CSF velocity images are reconstructed, and (3) accounting for venous drainage through routes other than the internal jugular veins (IJV).

1. The imaging plane for the blood flow measurements needs to be as perpendicular as possible to the four vessels entering the skull, the internal carotid and vertebral arteries, to avoid errors due to partial volume, and as close as possible to the skull base to avoid contributions from volume changes within the neck blood vessels [18]. In the vast majority of cases, an imaging plane at about the mid-C2 level meets these requirements [19].
2. To be able to add or subtract the CSF flow rates obtained with the low-venc scan from the blood flow rates obtained with high-venc scan, images from both scans need to be reconstructed at the same time points in the cardiac-cycle. Currently, that can be accomplished in different ways, one manufacturer enables selection of the reconstructed heart rate (i.e., projected HR) such that both the blood flow and the CSF flow images are reconstructed at the same time points within the cardiac-cycle. Another manufacturer provides the option of a dual-venc scan where the sampling of the high and low venc are interleaved. When the heartrates of the blood and CSF flow scans differ, time points in the two scans cannot be matched by a linear interpolation because changes in the cardiac cycle duration in response to a change in heartrate is not linear, the change in the cycle duration occurs primarily in the diastolic phase while the systolic phase is relatively unchanged.
3. Finally, estimation of the unmeasured venous drainage, i.e., the non-IJV venous drainage, can be achieved based on volume conservation, or a modified Monroe–Kellie principle, which states that, in steady state, the average ICV over the entire cardiac cycle is constant. Therefore, the average change in the ICV is zero. This implies that the integral of the net transcranial flow, i.e., the arterial inflow, the cranio-spinal CSF flow, and the measured (IJV) and the unmeasured venous outflow is zero [17].

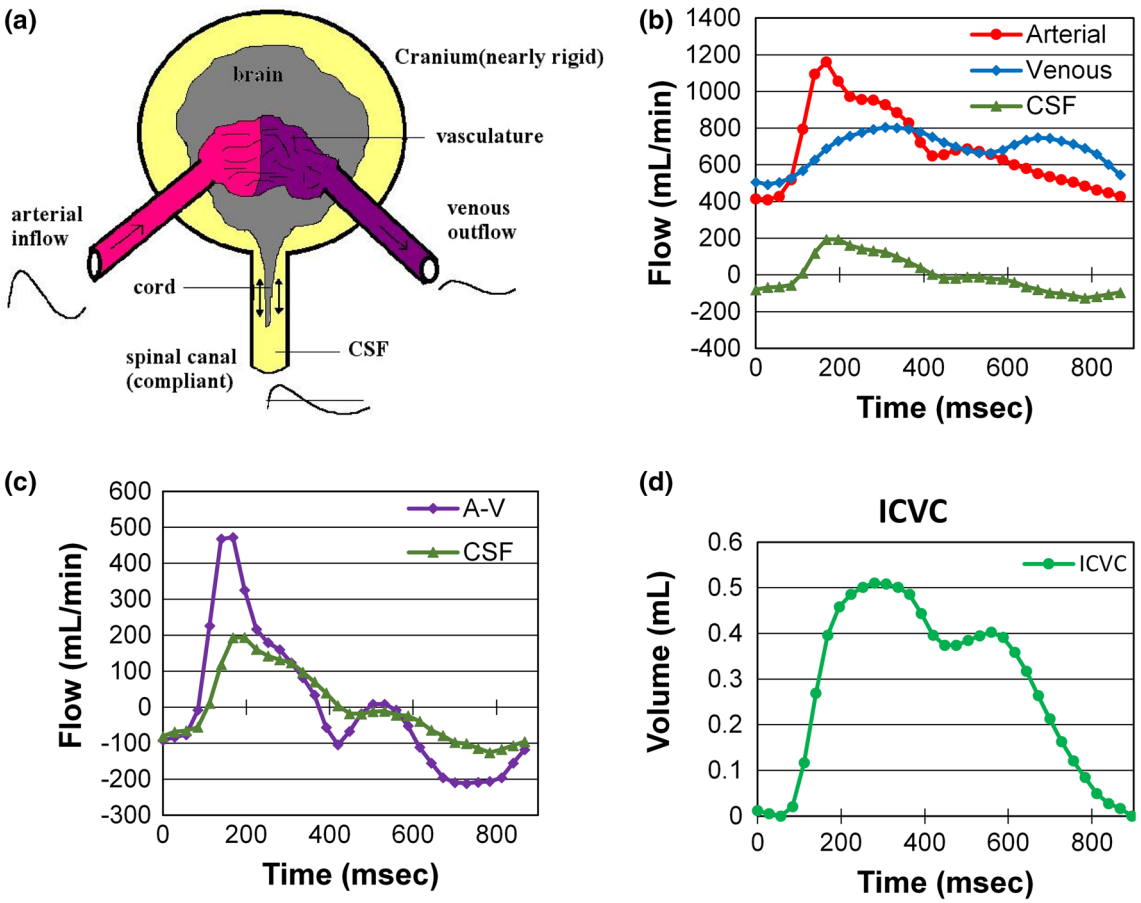

Fig. 1 **a** A simplified representation of the cranio-spinal system and the cranial inlets and outlets. **b** Volumetric flow rate waveforms of the arterial inflow, venous outflow, and the cranio-spinal CSF flow. **c** The CSF volumetric flow rate waveform plotted with respect to the arterial minus venous flow waveform. The fact that these two waveforms are not identical implies that the ICV is not constant. The CSF waveform follows the pattern of the net transcranial blood flow suggesting that the arterial minus venous flow drives the cranio-spinal CSF pulsation. **d** The intracranial volume change (ICVC) waveform during the cardiac cycle

In general, the cord contribution to the ICV change due to the cardiac-related displacement can be neglected.

Normally, in healthy subjects in the supine posture, the majority of the venous drainage (70–90% of the total arterial inflow) occurs through the IJV [20]. A large portion of the non-IJV drainage occurs through secondary channels such as the epidural, vertebral and deep cervical veins. In cases where venous flow in the secondary veins is present, it is depicted in the low-venc images as the venous flow velocities in the secondary veins are on the same order of the CSF velocities.

Figure 1a shows a simplified representation of the cranio-spinal system with its cranial inlet and outlets. The graph in Fig. 1b, shows example waveforms of the arterial, venous and CSF volumetric flow rates to and out from the cranium. The second graph shows the CSF flow waveform plotted with respect to the arterial minus venous flow. The fact that these two waveforms are not identical implies that the ICV is not constant during the cardiac cycle. Note that the cranio-spinal CSF flow "follows" the dynamics of the net transcranial blood flow. Hence, the arterial minus venous flow drives the cranio-spinal CSF pulsation. The final graph, Fig. 1d, shows the intracranial volume change (ICVC) waveform that is obtained from the arterial, venous and CSF flow waveforms shown in Fig. 1b. Often, for simplicity, venous outflow is assumed to be constant [21]. This leads to an overestimated maximal ICV change [22].

Principles of fluid dynamics are followed to calculate the ICP change during the cardiac-cycle (dICP) from its relation to the changes in the CSF pressure gradient [23]. The CSF pressure gradient waveform is derived from the CSF velocity images using the Naiver–Stokes relationship between temporal and spatial derivatives of the CSF velocities and the CSF pressure gradient [17]. The MRI method to measure the ICC has an advantage over the infusion methods as it is non-invasive, it utilizes the naturally occurring cardiac-related fluctuation in the ICV due to the pulsatile blood flow to the

brain, instead of an external infusion, and it does not alter the compliance state of the cranio-spinal compartments [17].

In summary, brain tissues are not compliant, therefore the brain does not contribute to the overall intracranial compliance. The structures that determine the ICC are the cranium and its linings, the dura matter, which are made of stiff materials that cannot be easily stretched or expand. The overall compliance of the intracranial compartment is thereby very small, on the order of a fraction of a milliliter per 1 mmHg, especially considering that the volume of the intracranial compartment is on the order of 1.5 liter. Much of the advancement in our understanding of the driving force of the cranio-spinal CSF dynamics and the ability to measure important hydrodynamic parameters, such as ICV and ICC, were achieved owing to novel MRI technology, velocity imaging.

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