Effects of cranioplasty in cerebral blood perfusion using quantification with 99m-Tc HMPAO SPECT-CT

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This work was previously presented at (International Congress Poster) Syndrome of the Trephined: evaluating brain perfusion before and after cranioplasty using 99m-Tc HMPAO and SPECT-CT Á. Galiana, S. Ruiz, I. Paredes, E. Gutiérrez, M. Tabuenca, M. Marín, E. Martínez, V. Godigna, D. Vega, J. Estenoz. 32nd Annual Congress of the European Association of Nuclear Medicine. Barcelona, October 2019.

Funding Information
Instituto de Salud Carlos III, Grant/Award Number: PI16/01939; European Union

Abstract

Background and Purpose: Syndrome of the trephined or sinking skin flap syndrome is an underdiagnosed condition of craniectomized patients that usually improves after cranioplasty. Among the pathophysiological theories proposed, the changes of cerebral blood perfusion (CBP) caused by cranial defects might have a role in the neurological deficiencies observed. We aim to assess the regional cortex changes in CBP after cranioplasty with Technetium 99m hexamethylpropylene-amine oxime (99mTc-HMPAO) SPECT-CT.

Methods: Twenty-eight craniectomized patients subject to cranioplasty were studied with 99mTc-HMPAO SPECT-CT in three different times, before cranioplasty, a week, and 3 months after. The images were processed with quantification software comparing CBP of 24 cortical areas with a reference area, and with a database of controls. A mixed effects model and T-Student were used.

Results: CBP increased significantly in both hemispheres after cranioplasty, either using ratio ($\beta = 0.019$, $p$-value = .030 first postsurgical SPECT-CT and $\beta = 0.021$, $p$-value = .015 in the second study, vs. presurgical) or Z-score ($\beta = 0.220$, $p$-value = .026 and $\beta = 0.279$, $p$-value = .005, respectively). Nine areas of the damaged side had a significant lower CBP ratio and Z-score than the undamaged. Posterior cingulate showed an increased CBP ratio (p-value = .034) and Z-score (p-value = .028) in the first postsurgical SPECT-CT. These posterior cingulate changes represent a 4.83% increase in ratio and 91.04% in Z-Score (p-value = .035 and .040, respectively).

Conclusion: CBP changes significantly in specific cortical areas after cranioplasty. Posterior cingulate changes might explain some improvements in attention impairments. SPECT-CT could be a useful tool to assess CBP changes in these patients and might be helpful in their clinical management.

Keywords
Cerebral blood perfusion, craniectomy, cranioplasty, HMPAO, SPECT-CT, syndrome of the trephined
INTRODUCTION

Sinking skin flap syndrome (SSFS) or syndrome of the trephined (SoT) is a difficult-to-diagnose complication of decompressive craniectomy performed for any cause. SSFS has variable clinical presentation with signs and symptoms, such as sunken skin flap in the site of the craniectomy, headache, motor weakness, and language deficits, which can begin in the days or months following craniectomy, in some cases after full or partial recovery. One of the most important characteristics of this syndrome is neurological improvement of many of these patients after the cranial defect is reconstructed with cranioplasty. Although the previously mentioned signs and symptoms constitute the classical definition of the syndrome, studies published in recent years have shown improvement in clinical and physiological parameters after cranioplasty, even in patients without symptoms of SSFS.

Such findings have changed the management of craniectomized patients and the use of cranioplasty has been implemented not only for aesthetic or protective reasons but also to improve patient functionality and prognosis.

The pathophysiology of SSFS is unknown, although different hypotheses have been published, most of them considering the main variable that seems to affect these patients, which is the influence of atmospheric pressure in the brain. Whether it directly harms the brain parenchyma, changes brain metabolism, alters brain blood perfusion, or affects cerebrospinal fluid (CSF) flow (or a combination of the aforementioned factors), the mechanisms underlying SSFS have not been elucidated to date.

CT or perfusion magnetic resonance has been used to examine cerebral blood perfusion (CBP) changes in these patients and establish different pathophysiological theories. In recent years, positron emission tomography has evolved to become the gold standard method for analyzing brain-blood hemodynamics, although measuring glucose metabolism is not exactly the same as measuring CBP. Moreover, quantification of those changes has typically been limited to brain hemispheres or lobes at most with no evaluation of different cortical regions.

In our study, we aimed to analyze changes in CBP in craniectomized patients before and after cranioplasty using Technetium-99 m hexamethylpropylene-amine oxime (Tc-99 m HMPAO) and SPECT-CT to assess changes in different cortical areas. This radiotracer is a specific tool to measure CBP, not only cerebral blood flow or metabolism, as in previous imaging studies.

METHODS

A total of 28 patients were selected for this study, all of whom had a craniectomy performed to control refractory high intracranial pressure and were due to cranioplasty between October 2016 and November 2019. Patients were scheduled to receive cranioplasty regardless of whether they had classical symptoms of SSFS as a procedure to improve their clinical situation. We recorded the demographic data of each patient, pathology leading to the craniectomy, date of cranioplasty, and any brain hemisphere damage.

Surgeries were scheduled a variable period of time after decompressive craniectomy, depending on the primary cause for decompression, reduction of brain swelling, and patient and surgeon preferences. As a general rule, procedures were performed after some patient rehabilitation. Autologous bone flaps were the first choice to reconstruct the cranial defects, and when not available, computer-designed polyetheretherketone or methacrylate implants were used.

To evaluate CBP, we used a hybrid imaging technique (SPECT-CT) for morphological imaging, as well as for attenuation correction. We employed Tc-99 m HMPAO as a radiopharmaceutical because it diffuses into neurons based on blood perfusion of the area. Ten to 20 minutes after injection, the radiopharmaceutical fixes to the neuron, and there is no intracerebral redistribution, resulting in a fixed representation of CBP. Each patient was scheduled for three separate studies performed at different timepoints, including before cranioplasty, 1 week after the surgery, and finally 3 months after surgery. Imaging studies were performed following the recommendations of the European Society of Nuclear Medicine guidelines. Patients were injected with a 925 MBq dose of Technetium-99 m HMPAO at rest and in decubitus in a quiet room 30–60 minutes before the scan was conducted. Images were acquired in a dual head gamma camera and CT scan (model NM/CT 640, General Electric Healthcare, USA). Images were reconstructed in a 128 × 128 matrix using high-resolution collimators. Processing was performed in Xeleris 4.0 Functional Imaging Workstation (General Electric Healthcare, USA) using filtered back projection reconstruction and Butterworth filtering (critical frequency 0.51, order 10).

Quantification was performed using QBrain software (General Electric Healthcare, U.S.A.), which was added to the Xeleris 4.0 Workstation. The regions of interest are automatically drawn by the software on the CBP image obtained by SPECT and then manually adjusted if needed to correct possible patient positioning issues. A ratio was calculated, comparing the 12 different cortical regions to one reference area, the pons, which was selected due to its location far from the cortical defects observed in these patients, which, in turn, is important to guarantee an adequate quantification of blood perfusion in the different studies. CBP in each cortical region was compared to a database of normal individuals included and validated for clinical use by the manufacturer in the QBrain software. A Z-score was obtained for each brain region that indicated the differences between the patient and normal CBP in each region (Figure 1).

Statistical analyses were performed using SAS software (version 9.4, SAS Institute Inc., 2012). Descriptive data are presented as the mean ± standard deviation for continuous variables, and categorical variables are expressed as absolute or relative frequencies. Two different methods of statistical analysis were performed for the same sample. First, we used a mixed model effects in which each patient was considered a random effect, while the brain hemisphere (damaged or undamaged) where the region studied was located and the moment in which the SPECT-CT was performed (presurgical, postsurgical 1 week and
3 months) were considered fixed effects, and the interaction between the moment and the brain hemisphere was evaluated. This model reliably determines the areas where changes are observed and the value of such variations. Second, we used a T-Student for related samples to assess the variations of CBP in each patient at two different timepoints to clearly determine the magnitude of those changes.

This study was revised and approved by the ethical committee of the Hospital Universitario 12 de Octubre (Reference: Committee for Clinical Research number: 16/361). Informed consent to participate and publication was obtained from all participants in this study.

RESULTS

A total of 28 patients were included in this study (Table 1): 17 male (60.71%) and 11 female (39.29%). The age of the patients ranged from 16 to 81 years with a mean age of 39.81 ± 15.93 years. Sixteen patients (57.14%) suffered head trauma as the primary brain injury leading to craniectomy, 5 (17.86%) had a stroke, 5 (17.86%) had intraparenchymal hemorrhage, 1 had subarachnoid hemorrhage (3.57%), and 1 had encephalitis (3.57%). All patients had a unilateral cranial defect, 16 (57.14%) on the right side of the skull and 12 (42.86%) on the left side. The average interval between craniectomy and cranioplasty was 43.66 weeks (±30.73).

Results are shown for both the ratio and Z-score for each hemisphere as a whole, as well as for the 12 regions in each hemisphere. We referred to the damaged side as the hemisphere where the cranioplasty was performed, and we referred to the undamaged side as the other hemisphere.

TABLE 1  Characteristics of the participants

| Variable                                | Value          |
|-----------------------------------------|----------------|
| Age (years)                             | 39.89 ± 15.93 |
| Sex (male), n (%)                       | 17 (60.71%)    |
| Cause of the craniectomy, n (%)         |                |
| Intraparenchymal hemorrhage             | 5 (17.86%)     |
| Malignant stroke                        | 5 (17.86%)     |
| Trauma                                  | 16 (57.14%)    |
| Encephalitis                            | 1 (3.57%)      |
| Subarachnoid hemorrhage                 | 1 (3.57%)      |
| Damaged side, n (%)                     |                |
| Left                                    | 12 (42.86%)    |
| Right                                   | 16 (57.14%)    |
| Interval between surgeries in weeks     | 43.66 ± 30.73  |
| Ventriculoperitoneal shunt, n (%)       | 3 (10.71%)     |
| Complications, n (%)                    |                |
| Infections (total)                      | 3 (10.71%)     |
| Infection of the site of craniectomy    | 2 (7.14%)      |
| Postcranioplasty infection              | 1 (3.57%)      |

Note: All data represent mean ± standard deviation unless otherwise indicated; n = number of participants.

Regarding both hemispheres as a whole, our results with a mixed effects model showed a statistically significant increase in CBP in both hemispheres after cranioplasty, both in ratio ($\hat{\beta} = .019, p\text{-value} = .030$) in the SPECT-CT a week after surgery and $\beta = .021, p\text{-value} = .015$ in the
Visualization of the cerebral blood perfusion (CBP) on a presurgical SPECT-CT where the functional images are presented on a template of the normal brain. Defects and reduced perfusion in the frontal, parietal, and parietal lobes of the right hemisphere are evident in the images and consequently provoke reduced cerebral blood perfusion ratios (patient column) and Z-scores. This pattern of cortical damage with preservation of CBP in medial regions of the cortex as well as contralateral hemisphere is found throughout the study subjects. S, superior; I, inferior; L, left; R, right; A, anterior; P, posterior.

In the analysis for each of the 12 areas, nine of the damaged hemispheres (prefrontal lateral and medial, sensorimotor, occipital lateral, primary visual, precuneus, and both temporal lateral and mesial) presented a significantly lower ratio (Table 2 and Figure 3) and Z-score (Table 3 and Figure 4) for CBP compared to the undamaged side.

Regarding measurement of CBP ratios using a mixed effects model, prefrontal lateral and anterior cingulate in both hemispheres exhibited an average increase in CBP of 0.027 and 0.035 units of ratio, respectively, in the second SPECT-CT compared to the presurgical study (p-values = .026 and .279, p-value = .005, respectively). The precuneus only presented increased perfusion by 0.052 units in the imaging study performed 3 months after cranioplasty (p-value = .048). The posterior cingulate increased by 0.042 units (interaction p-value = .034) in the second SPECT-CT. Percentage variation of average CBP ratios (Table 4) was statistically significant only in cortical regions of the damaged hemisphere and in the comparison between the presurgical and the first postsurgical study. The prefrontal medial had a CBP ratio increase of 2.48% (p-value = .047), anterior cingulate 3.94% increment (p-value = .026), and posterior cingulate had the highest raise with 4.83% (p-value = .035). No statistically significant results were found in the comparison between the presurgical and the 3 months postsurgical study, although the highest variation was found on the posterior cingulate with an increase of 5.58% (p-value = .064).

In the assessment of Z-score with the mixed effects model in the 12 brain regions studied, the precuneus showed a significant increase in both hemispheres of 0.429 and 0.821 in the second and third SPECT-CT, respectively, versus presurgical measurements (p-values = .011 and .003, respectively). The occipital lateral decreased by 0.687 units in only the damaged hemisphere in the third SPECT-CT (interaction p-value = .041), while the posterior cingulate increased by 0.416 units in only the damaged hemisphere in the second SPECT-CT (interaction p-value = .028). Notably, the posterior cingulate was the only area where the interaction of the damaged side and the second SPECT-CT had significant results for both the ratio and Z-score. Percentage variation of average Z-score in each area (Table 5) was statistically significant mostly in cortical regions of the damaged hemisphere and only when comparing the presurgical and the first postsurgical study, the prefrontal medial had a Z-score increment of 31.59% (p-value = .028), anterior cingulate 96.16% (p-value = .037), posterior cingulate 91.04% (p-value = .040), and temporal mesial where relevant differences were
TABLE 2  Results of mixed models. Significant cerebral blood perfusion ratios variations by areas, compared with the pons (reference area)

| Brain area       | Beta  | Standard Error | p-value |
|------------------|-------|----------------|---------|
| **Prefrontal lateral** |       |                |         |
| Intercept        | 1.015 | 0.024          | .0000   |
| Second SPECT-CT | 0.027 | 0.011          | .0201*  |
| Third SPECT-CT  | 0.019 | 0.016          | .2401   |
| Damaged side vs. undamaged side | -0.081 | 0.028          | .0049*  |
| **Prefrontal medial** |       |                |         |
| Intercept        | 1.014 | 0.022          | .0000   |
| Second SPECT-CT | 0.020 | 0.011          | .0824   |
| Third SPECT-CT  | 0.020 | 0.016          | .2138   |
| Damaged side     | -0.034 | 0.009          | .0003*  |
| **Sensorimotor** |       |                |         |
| Intercept        | 1.074 | 0.029          | .0000   |
| Second SPECT-CT | 0.021 | 0.015          | .1528   |
| Third SPECT-CT  | 0.029 | 0.017          | .0897   |
| Damaged side vs. undamaged side | -0.093 | 0.035          | .0084*  |
| **Occipital lateral** |       |                |         |
| Intercept        | 1.117 | 0.025          | .0000   |
| Second SPECT-CT | 0.029 | 0.014          | .0535   |
| Third SPECT-CT  | 0.018 | 0.020          | .3592   |
| Damaged side vs. undamaged side | -0.059 | 0.027          | .0329*  |
| **Primary visual** |      |                |         |
| Intercept        | 1.284 | 0.029          | .0000   |
| Second SPECT-CT | -0.005 | 0.014       | .7183   |
| Third SPECT-CT  | 0.021 | 0.023          | .3671   |
| Damaged side vs. undamaged side | -0.069 | 0.021          | .0023*  |
| **Parietal inferior** |    |                |         |
| Intercept        | 1.104 | 0.039          | .0000   |
| Second SPECT-CT | 0.009 | 0.016          | .5686   |
| Third SPECT-CT  | -0.003 | 0.018        | .8486   |
| Damaged side vs. undamaged side | -0.094 | 0.065          | .1504   |
| **Parietal superior** |       |                |         |
| Intercept        | 1.082 | 0.025          | .0000   |
| Second SPECT-CT | 0.019 | 0.015          | .2070   |
| Third SPECT-CT  | 0.028 | 0.016          | .0918   |
| Damaged side vs. undamaged side | -0.090 | 0.029          | .0025*  |

(Continues)

**DISCUSSION**

The Grant and Norcross article from 1939 is usually cited as the first known reference of the “Syndrome of the Trephined,” describing a
deterioration of craniectomized patients suffering from a combination of headache, dizziness, undue fatigability, vague discomfort at the site of the cranial defect, a feeling of apprehension and insecurity, mental depression, and intolerance to vibration. In this study, the authors stated the difficulties in detecting and identifying SoT for those symptoms, where it is not always possible to differentiate them from a possible deterioration of the primary brain injury. Notably, this paper references previous works from the late 19th and early 20th centuries, which suggests the possibility that the first definition of this syndrome was made decades earlier.

Another classic paper that is frequently cited is the work of Yamaura and colleagues from Chiba University of Japan in 1977. In this work, 33 craniectomized patients were classified according to the exterior appearance of the cranial defect (sinking, flat, full, or bulging) and the severity of their neurological deterioration. Nine patients presented neurological improvement after cranioplasty, especially in the group classified as having moderate neurological deficits. This study was also one of the first to assess cranial fluid dynamics, which in this case examined the CSF opening pressure using a lumbar puncture before and after cranioplasty. In the patients studied, the opening pressure measured prior to surgery was low (≤80 mmH₂O) in sinking and flat skin patients, and more significantly, in all patients who had an improved neurological condition, CSF pressure increased to normal while remaining low in cases with no clinical improvement. This work concluded that atmospheric pressure and subsequent damage to the brain parenchyma are the most plausible causes of the "syndrome of the sinking flap" rather than the "syndrome of the trephine" referred to in earlier works.

In 2016, Ashayeri published an extensive review of 58 patients with SoT in which different imaging techniques were employed to evaluate CSF flow and CBP using MRI and CT. In the cases presented, there was an increase in CBP after cranioplasty, although no clear conclusions about the possible utility of such techniques in diagnosing or evaluating the prognosis were established. Moreover, this paper clearly explains and recompiles the four primary pathophysiological theories that have been postulated to date: the effect of atmospheric pressure in the brain parenchyma and local blood and CSF flow; changes in CBP both at the site of the defect and in distant regions; CSF dynamics and pressure; and altered cerebral metabolism.7

To the best of our knowledge, in 2017, Halani and colleagues published the most extensive review to date of CBP changes before and after cranioplasty using CT (dynamic CT, Xenon CT), transcranial Doppler (TCD), perfusion magnetic resonance imaging, SPECT, and positron emission tomography.8 Two hundred and three patients were included and examined before and after cranioplasty, showing increased CBP after cranioplasty in the damaged hemisphere, and nine out of the 21 studies included also reported increased CBP or glucose metabolism activity (Positron Emission Tomography with 18-fluorodeoxyglucose) on the side not affected by cranioplasty.

Stiver et al. performed perfusion CT scans on patients with pre-cranioplasty monoparesia, which showed hypoperfusion in the area adjacent to the cranial defect that was resolved after cranioplasty.9 In 2006, Sakamoto et al. described a patient with symptoms compatible with SoT who was evaluated before and after cranioplasty with a CT perfusion scan, which showed an increase in CBP after the procedure.9 Sarubbo et al. studied changes in CBP before and after cranioplasty (7 days and 3 months, respectively), showing an increase in CBP, although less important at the 3-month study, suggesting that the changes observed begin soon after cranioplasty and may even be temporary.10

In our center, Paredes et al. assessed CBP in 49 patients, demonstrating an increase in CBP from 101.86 to 117.17 ml/min/100 g/min and from 128.14 to 145.73 ml/100 g/min on the damaged and undamaged sides,
### TABLE 3

Results of mixed models. Significant cerebral blood perfusion variations by areas, comparing patients and normal population (Z-score)

| Brain area     | Beta  | Standard error | p-value |
|----------------|-------|----------------|---------|
| Prefrontal lateral |       |                |         |
| Intercept       | -1.065| 0.325          | .0013   |
| Second SPECT-CT | 0.303 | 0.161          | .0618   |
| Third SPECT-CT  | 0.265 | 0.222          | .2331   |
| Damaged side vs. undamaged side | -1.118 | 0.361          | .0023*  |
| Prefrontal medial |     |                |         |
| Intercept       | -0.832| 0.228          | .0004   |
| Second SPECT-CT | 0.293 | 0.152          | .0557   |
| Third SPECT-CT  | 0.246 | 0.218          | .2613   |
| Damaged side vs. undamaged side | -0.450 | 0.113          | .0001*  |
| Sensorimotor    |       |                |         |
| Intercept       | -0.832| 0.228          | .0004   |
| Second SPECT-CT | 0.293 | 0.152          | .0557   |
| Third SPECT-CT  | 0.246 | 0.218          | .2613   |
| Damaged side vs. undamaged side | -0.450 | 0.113          | .0001*  |
| Occipital lateral |      |                |         |
| Intercept       | 0.945 | 0.370          | .0116   |
| Second SPECT-CT | 0.340 | 0.197          | .0857   |
| Third SPECT-CT  | 0.660 | 0.360          | .0684   |
| Damaged side vs. undamaged side | -0.832 | 0.394          | .0363*  |
| Second SPECT-CT | 0.093 | 0.246          | .7047   |
| Third SPECT-CT  | 0.292 | 0.247          | .2397   |
| Damaged side vs. undamaged side | -1.107 | 0.347          | .0017*  |
| Parietal superior |       |                |         |
| Intercept       | 0.788 | 0.349          | .0254   |
| Second SPECT-CT | 0.093 | 0.246          | .5524   |
| Third SPECT-CT  | 0.241 | 0.204          | .2394   |
| Damaged side vs. undamaged side | 0.028 | 0.119          | .8101   |
| Anterior cingulate |     |                |         |
| Intercept       | -0.452| 0.245          | .0670   |
| Second SPECT-CT | 0.378 | 0.173          | .0310*  |
| Third SPECT-CT  | 0.241 | 0.204          | .2394   |
| Damaged side vs. undamaged side | 0.028 | 0.119          | .8101   |
| Posterior cingulate |     |                |         |
| Intercept       | 0.780 | 0.226          | .0007   |
| Second SPECT-CT | 0.131 | 0.220          | .1167   |
| Third SPECT-CT  | 0.460 | 0.291          | .2852   |
| Damaged side vs. undamaged side | -0.176 | 0.164          | .0001*  |
| Precuneus       |       |                |         |
| Intercept       | 1.511 | 0.265          | .0000   |
| Second SPECT-CT | 0.429 | 0.168          | .0117*  |
| Third SPECT-CT  | 0.821 | 0.272          | .0130*  |
| Damaged side vs. undamaged side | -0.758 | 0.192          | .0001*  |
| Temporal lateral |      |                |         |
| Intercept       | -0.418| 0.326          | .2019   |
| Second SPECT-CT | 0.179 | 0.172          | .2995   |
| Third SPECT-CT  | 0.255 | 0.224          | .2571   |
| Damaged side vs. undamaged side | -1.221 | 0.391          | .0211*  |
| Temporal mesial |       |                |         |
| Intercept       | 0.532 | 0.277          | .0573   |
| Second SPECT-CT | 0.468 | 0.235          | .0479   |
| Third SPECT-CT  | 0.110 | 0.286          | .6991   |
| Damaged side vs. undamaged side | -1.228 | 0.327          | .0002*  |

*First SPECT-CT as reference for second and third SPECT-CT

bThe results of the interactions between the moment and the brain hemisphere are only included in the areas of the brain where they were significant.

*Significance for p-value < 0.05
FIGURE 4  Graphics representing average variations of Z-scores (horizontal axis) for each of the 12 different cortical areas studied. Two lines are drawn for each cortical area representing the damaged and undamaged side of the brain. The lines have three points representing the different SPECT-CT studies. The first point represents the presurgical SPECT-CT, the second the first postsurgical study (1 week after the cranioplasty), and the third the last SPECT-CT (3 months after).

respectively. CBP improvement was observed in all craniectomized patients, regardless of whether they presented with SoT symptoms. In the same study, no statistically significant clinical relationship was observed between those results and clinical improvement, although a greater increase in CBP was identified in patients with a better clinical outcome.

Shahid and colleagues studied CBP in brain lobes and basal ganglia 1 week before and 3 months after cranioplasty. CBP assessment was obtained with SPECT-CT using technetium-99 m ethyl cysteinate dimer (99 mTc-ECD), whose pharmacokinetics differ slightly from 99 mTc-HMPAO. They found that CBP increased after cranioplasty in the frontal and occipital lobes and decreased in the other lobes, although statistically significant changes were only found in occipital and basal ganglia regions. The decrease in blood flow in the parietal, temporal, and basal ganglia was attributed to redistribution of the CBP after cranioplasty. Matsumura presented a case in 1996 of a young child with a cranial defect in the right parietofrontal region. The young patient was studied before and after reconstructive surgery using 99 mTc-HMPAO, which showed a decrease in CBP in the damaged area that subsequently normalized.

To the best of our knowledge, we present the first series of patients whose CBP was evaluated using 99 mTc HMPAO SPECT-CT. Moreover, we did not find other studies analyzing blood perfusion changes at the regional level or comparing those variations to a normal population, as we have done using the normal brain database in our quantification software.

First, we must consider that we are not measuring absolute variations in blood flow but rather changes in the ratios between the different brain regions using the pons as a reference. Quantification using ratios has one major advantage: general blood perfusion alterations in the whole brain also alter the reference area used to compare the cortex; as such, we consider those values to be more accurate than absolute values. Another aspect of the study worth considering is that the damaged side of the brain is prone to possible quantification errors by the software due to the anatomical damage that these patients suffer, which is especially significant in parietal and frontal lobes, where parenchymal damage is more frequent.

We identified an increase in CBP on both sides of the brain after cranioplasty, and the ratios increased bilaterally in eight of 12 regions examined in the second study and in three regions in the third SPECT-CT, which was more significant in the evaluation performed 3 months after surgery. This difference was observed both in the ratios of CBP and Z-score, which is consistent with published evidence using other imaging techniques and adds more evidence indicating that CBP increases in both hemispheres after cranioplasty, and that CBP changes seem to play a key role in the pathophysiology of SoT.

Regarding specific regions, the general pattern evidenced an increase in CBP after surgery, especially in the second study, while the tendencies in the third study were more variable. For example, temporal regions exhibited a decrease in CBP, even lower than in the presurgical examination, which, according to Shahid, might indicate redistribution of CBP from the temporal lobes to other areas of the brain that are typically damaged. In our case, we did not observe the same results in the parietal lobes.

The cingulate cortex demonstrated a particular pattern on the damaged side, since both anterior and posterior regions of this cortical area are the only regions where the blood perfusion ratio in the week after cranioplasty reaches higher ratios than the undamaged side of the brain both in ratios and Z-scores. The posterior cingulate of the damaged side is the only area of the brain that exhibited a statistically significant increase in blood perfusion ratio in the second study, both in
### TABLE 4 Percentage of ratios change between studies at different timepoints

| Area          | Ratio Percentage Difference of Ratio | p-value | % Δ 1-3 | p-value |
|---------------|--------------------------------------|---------|---------|---------|
| Prefrontal lateral damaged | 2.57 | .661 | 4.12 | .832 |
| Prefrontal lateral undamaged | 0.95 | .117 | 0 | .999 |
| Prefrontal medial damaged | 2.48 | .047* | 1.19 | .507 |
| Prefrontal medial undamaged | 4.32 | .304 | 4.91 | .319 |
| Sensorimotor damaged | 0.6 | .786 | 2.32 | .284 |
| Sensorimotor undamaged | 3.74 | .079 | 3.09 | .098 |
| Occipital lateral damaged | 0 | .959 | 0 | .955 |
| Occipital lateral undamaged | 3.56 | .998 | 4.18 | .067 |
| Primary visual damaged | 0 | .986 | 1.75 | .377 |
| Primary visual undamaged | 0.86 | .559 | 3.85 | .106 |
| Parietal inferior damaged | 0.39 | .848 | 0.79 | .826 |
| Parietal inferior undamaged | 1.52 | .462 | 2.42 | .575 |
| Parietal superior damaged | 4.25 | .076 | 1.21 | .567 |
| Parietal superior undamaged | -0.92 | .629 | 2.21 | .198 |
| Anterior cingulate damaged | 3.94 | .026* | 1.34 | .514 |
| Anterior cingulate undamaged | 2 | .285 | 1.52 | .501 |
| Posterior cingulate damaged | 4.83 | .035* | 5.58 | .064 |
| Posterior cingulate undamaged | 1.31 | .509 | 4.11 | .159 |
| Precuneus damaged | 2.41 | .166 | 3.25 | .163 |
| Precuneus undamaged | 0.23 | .905 | 3.12 | .195 |
| Temporal lateral damaged | -0.85 | .675 | -1.17 | .671 |
| Temporal lateral undamaged | 2.08 | .165 | 2.18 | .189 |
| Temporal mesial damaged | 2.77 | .196 | -0.21 | .953 |
| Temporal mesial undamaged | 0.48 | .882 | 0.48 | .882 |

Note: Statistically significant results are highlighted (*).

### TABLE 5 Percentage of Z-score change between studies at different timepoints

| Area          | Z-score Percentage Difference of Ratio | p-value | % Δ 1-3 | p-value |
|---------------|--------------------------------------|---------|---------|---------|
| Prefrontal lateral damaged | 12.97 | 0.913 | 28.02 | 0.897 |
| Prefrontal lateral undamaged | 24.81 | 0.127 | -8.27 | 0.101 |
| Prefrontal medial damaged | 31.59 | 0.028* | 15.75 | 0.465 |
| Prefrontal medial undamaged | 28.45 | 0.444 | 39.83 | 0.425 |
| Sensorimotor damaged | 3.34 | 0.871 | 22.29 | 0.301 |
| Sensorimotor undamaged | 17.42 | 0.083 | 10.26 | 0.096 |
| Occipital lateral damaged | -9.91 | 0.669 | -2.32 | 0.939 |
| Occipital lateral undamaged | 36.08 | 0.092 | 69.94 | 0.068 |
| Primary visual damaged | 19.81 | 0.654 | 65.81 | 0.293 |
| Primary visual undamaged | 10.09 | 0.512 | 36.69 | 0.136 |
| Parietal inferior damaged | 3.4 | 0.856 | 18.82 | 0.582 |
| Parietal inferior undamaged | 17.81 | 0.403 | 17.95 | 0.371 |
| Parietal superior damaged | 5.87 | 0.406 | 2.66 | 0.711 |
| Parietal superior undamaged | -9.99 | 0.752 | 25.54 | 0.348 |
| Anterior cingulate damaged | 96.16 | 0.037* | 39.31 | 0.561 |
| Anterior cingulate undamaged | 8.41 | 0.241 | 5.91 | 0.468 |
| Posterior cingulate damaged | 91.04 | 0.040* | 92.23 | 0.064 |
| Posterior cingulate undamaged | 16.79 | 0.568 | 58.97 | 0.167 |
| Precuneus damaged | 61.85 | 0.034* | 68.3 | 0.151 |
| Precuneus undamaged | 1.59 | 0.911 | 27.53 | 0.198 |
| Temporal lateral damaged | -7.58 | 0.651 | -10.06 | 0.636 |
| Temporal lateral undamaged | 21.09 | 0.251 | 29.1 | 0.157 |
| Temporal mesial damaged | 5.28 | 0.216 | -0.99 | 0.848 |
| Temporal mesial undamaged | 88.01 | 0.046* | 53.73 | 0.312 |

Note: Statistically significant results are highlighted (*).

The percentage of variations in CBP is below 5% in case of ratios (Table 4) and mostly perceptible with quantification analysis that is nowadays a common tool. To our knowledge, this is the first time that significant changes in CBP have been identified in a specific region of the brain in this patient population.

In a review article by Leech and Sharp,14 the authors describe theories that might explain the functionality of the posterior cingulate, as well as its implications in different diseases.12 In functional studies, the posterior cingulate exhibits an increased metabolism of approximately 40% greater than the surrounding parenchyma in the basal state, and its metabolic activity seems to fluctuate significantly less than other areas in different cognitive states. The functions of this area are mostly related to attention and spatial memory, being an important node in the default mode network that activates during internal tasks, such as memory retrieval, planning, or autobiographical memories. Different diseases and circumstances have been shown to produce changes in posterior cingulate function, such as ageing, Alzheimer’s disease, autism, and depression. Traumatic brain injury induces a reduction in metabolism and blood perfusion in the damaged area, which is related to attention deficits with difficulties sustaining attention, producing attentional lapses and decreased cognitive performance. Although we did not perform any clinical evaluation in this study, dysfunction of this area was related to similar symptoms in craniectomized patients and could serve as evidence for further studies of the function of this brain region.

We are aware of several limitations in our study, the most relevant being the possible miscalculation of regional CBP due to anatomical anomalies. This limitation is hardly solvable due to the heterogeneity of anatomical alterations among patients and timepoints. However, all the imaging studies have been processed with the same software and parameters, and the relevant findings of regional CBP alterations are mostly found in areas far from the harmed regions.

Other relevant limitations are related to the heterogeneous patient population in our study, with different causes leading to decompression and the one performed 3 months after cranioplasty (3).
ognitive, and cognitive outcome. J Neurosurg 2018;128:229-35.
12. Matsumura H, Shigehara K, Ueno T, et al. Cranial defect and decrease in cerebral blood flow resulting from deep contact burn of the scalp in the neonatal period. Burns 1996;22:560-5.
13. Isago T, Nozaki M, Kikuchi Y, et al. Sinking skin flap syndrome of the trephined: a review. Br J Neurosurg 1990;4:583-5.
14. Shahid AH, Mohanty M, Singla N, et al. The effect of cranioplasty following decompressive craniectomy on cerebral blood perfusion, neurological, and cognitive outcome. J Neurosurg 2018;128:229-35.
15. Leech R, Sharp DJ. The role of the posterior cingulate cortex in cognition and disease. Brain 2014;137:12-32.

ACKNOWLEDGEMENTS AND DISCLOSURES
Authors would like to thank all the staff of the departments involved in this study. Special mention to the secretary of the Nuclear Medicine Department, María Soledad Labanda, whose dedication and consistency in keeping the patients records and studies has been essential to the development of this study. The main text was reviewed by American Journal Editors in March 2021 for previous submissions (verification code OD84-4574-6BA4-7F70-8392), although significant changes have been made since. The authors declare no conflict of interest.

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REFERENCES
1. Annan M, De Toffol B, Hommet C, et al. Sinking skin flap syndrome (or Syndrome of the trephined): a review. Br J Neurosurg 2015;29: 314-8.
2. Paredes I, Castaño AM, Cepeda S, et al. The effect of cranioplasty on cerebral hemodynamics as measured by perfusion computed tomography and doppler ultrasonography. J Neurotrauma 2016;33: 1586-97.
3. Di Rienzo A, Colasanti R, Glati M, et al. Sinking flap syndrome revisited: the who, when and why. Neurosur Rev 2020;43:323-35.
4. Halani SH, Chu JK, Malcolm JG, et al. Effects of cranioplasty on cerebral blood flow following decompressive craniectomy: a systematic review of the literature. Neurosurgery 2017;81:204-16.
5. Grant FC, Norcross NC. Repair of cranial defects by cranioplasty. Ann Surg 1939;110:488-512.
6. Yamaura A, Makino H. Neurological deficits in the presence of the sinking skin flap following decompressive craniectomy. Neurol Med Chir (Tokyo) 1977;17:43-53.
7. Ashayeri K, Jackson EM, Huang J, et al. Syndrome of the trephined: a systematic review. Neurosurgery 2016;79:525-34.
8. Stiver SJ, Winterrman M, Manley GT. Reversible monoparesis following decompressive hemicraniectomy for traumatic brain injury. J Neurosurg 2008;109:245-54.
9. Sakamoto S, Eguchi K, Kiura Y, et al. CT perfusion imaging in the syndrome of the sinking skin flap before and after cranioplasty. Clin Neurol Neurosurg 2006;108:583-5.
10. Sarubbo S, Latini F, Ceruti S, et al. Temporal changes in CT perfusion values before and after cranioplasty in patients without symptoms related to external decompression: a pilot study. Neuroradiology 2014;56:237-43.
11. Shahid AH, Mohanty M, Singla N, et al. The effect of cranioplasty following decompressive craniectomy on cerebral blood perfusion, neurological, and cognitive outcome. J Neurosurg 2018;128:229-35.
12. Matsumura H, Shigehara K, Ueno T, et al. Cranial defect and decrease in cerebral blood flow resulting from deep contact burn of the scalp in the neonatal period. Burns 1996;22:560-5.
13. Isago T, Nozaki M, Kikuchi Y, et al. Sinking skin flap syndrome: a case of improved cerebral blood flow after cranioplasty. Ann Plast Surg 2004;53:288-92.
14. Leech R, Sharp DJ. The role of the posterior cingulate cortex in cognition and disease. Brain 2014;137:12-32.

How to cite this article: Galiana Á, Ruiz S, Alén JF, Gómez Grande A, Panero I, Vega D, et al. Effects of cranioplasty in cerebral blood perfusion using quantification with 99mTc HMPAO SPECT-CT. J Neuroimaging. 2023;33:174–183. https://doi.org/10.1111/jon.13058