ORIGINAL RESEARCH

Neurovascular/Stroke Imaging

Efficacy Assessment of Cerebral Perfusion Augmentation Through Functional Connectivity in an Acute Canine Stroke Model

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ABSTRACT

BACKGROUND AND PURPOSE: Ischemic stroke disrupts functional connectivity within the brain's resting-state networks (RSNs), impacting recovery. This study evaluates the effects of NEH (Norepinephrine and Hydralazine), a cerebral perfusion augmentation therapy, on RSN integrity in a hyper-acute canine stroke model.

MATERIALS AND METHODS: Fifteen adult purpose-bred mongrel canines, divided into treatment and control (natural history) groups, underwent endovascular induction of acute middle cerebral artery occlusion (MCAO). Post-occlusion, the treatment group received intra-arterial Norepinephrine (0.1-1.52 μg/kg/min, adjusted for 25-45 mmHg above baseline mean arterial pressure) and Hydralazine (20mg). Resting-state fMRI data were acquired with a 3.0 T scanner using a BOLD-sensitive EPI sequence (TR/TE=1400 ms/20ms, 2.5 mm slices, 300 temporal positions). Preprocessing included motion correction, spatial smoothing (2.5 mm FWHM), and high-pass filtering (0.01 Hz cutoff). Functional connectivity within RSNs were analyzed through group-level independent component analysis (ICA) and weighted whole-brain ROI-to-ROI connectome, pre- and post-MCAO.

RESULTS: NEH therapy significantly maintained connectivity post-MCAO in the Higher-order Visual and Parietal RSNs, as evidenced by thresholded statistical mapping (TFCE p-corr > 0.95). However, this preservation was network-dependent, with no significant changes in the Primary Visual and Sensorimotor networks.

CONCLUSIONS: NEH demonstrates potential as a proof-of-concept therapy for maintaining RSN functional connectivity following ischemic stroke, emphasizing the therapeutic promise of perfusion augmentation. These insights reinforce the role of functional connectivity as a measurable endpoint for stroke intervention efficacy, suggesting clinical translatability for patients with insufficient collateral circulation.

ABBREVIATIONS: NEH = Norepinephrine and Hydralazine; RSN = Resting-State Network; ICA = Independent Component Analysis; rsfMRI = resting-state Functional Magnetic Resonance Imaging; MCAO = Middle Cerebral Artery Occlusion; TFCE = Threshold-Free Cluster Enhancement.

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SUMMARY SECTION

PREVIOUS LITERATURE: Current understanding emphasizes the vulnerability of resting-state networks (RSNs) to ischemic stroke and the potential of perfusion augmentation strategies to influence post-stroke recovery. The efficacy of such treatments in preserving functional connectivity within RSNs remains a key area of investigation.

KEY FINDINGS: NEH therapy preserved functional connectivity in Higher-order Visual and Parietal networks post-stroke in canines, with the treatment effect proving network-specific.

KNOWLEDGE ADVANCEMENT: This study advances the concept of targeted perfusion augmentation, demonstrating NEH's role in neural network protection and its potential for clinical stroke intervention.

INTRODUCTION

Ischemic stroke, a leading cause of mortality and chronic disability worldwide, imposes a significant challenge for both acute management and long-term rehabilitation.[1,2] The intricate pathophysiology of stroke, primarily the abrupt disruption of cerebral blood flow leading to neuronal death, necessitates advancements in therapeutic strategies beyond the acute phase, aiming to restore and enhance neurological function and quality of life.[3]

Recent strides in neuroimaging, particularly resting-state functional Magnetic Resonance Imaging (rsfMRI), have opened new avenues in understanding the brain's intrinsic functional connectivity.[2-4] This non-invasive technique provides insights into the spontaneous neural activity across various resting-state networks (RSNs), which are critical for various cognitive and motor functions.[4-8] The dynamic changes in these networks post-stroke are increasingly recognized for their potential implications in predicting recovery trajectories and guiding rehabilitation efforts.[4-12]

Building upon this premise, our study introduces a therapeutic strategy aimed at augmenting cerebral perfusion in the acute phase of ischemic stroke. Utilizing a combination of Norepinephrine and Hydralazine (NEH) administered intra-arterially, we hypothesize that this intervention can modulate the functional connectivity within key RSNs, thereby preserving or potentially enhancing neurologic function. This rationale is rooted in the dual mechanism of NEH – elevating systemic blood pressure to improve perfusion and directly inducing vasodilation to augment blood flow to ischemic regions, including the penumbra, which is critically vulnerable in the aftermath of a stroke.

This investigation employs a canine model of hyper-acute ischemic stroke, induced via middle cerebral artery occlusion (MCAO), to examine the effects of NEH therapy on functional connectivity across identified RSNs through rsfMRI.[13] Our study is poised to contribute significantly to the understanding of cerebral perfusion augmentation as a therapeutic mechanism, potentially setting the stage for translational applications in stroke recovery and rehabilitation strategies.

In focusing on the alterations in RSNs, we aim not only to highlight the neuroprotective potential of NEH therapy but more importantly to underscore the relevance of functional connectivity as a critical endpoint in evaluating the efficacy of stroke interventions. Through this research, we aspire to enrich the dialogue within the neuroscientific community regarding the integration of advanced imaging techniques and pharmacological innovations in crafting the next generation of stroke therapies.

MATERIALS AND METHODS

Experimental Design and Canine Model

Fifteen adult purpose-bred mongrel canines (average weight 25 ± 5 kg, comprising 12 females and 3 males, with an average age of 4.2 ± 3.3 years) were selected to investigate the neuroprotective effects of cerebral perfusion augmentation via NEH on rsfMRI-determined functional connectivity. The fifteen animals were split into a control and treatment group, with 7 per group due to the expiration of a subject. The study spanned two days, starting with baseline MRI scans under general anesthesia, which was meticulously maintained using a combination of propofol (25 μg/kg/min) for systemic sedation, rocuronium bromide (0.4-0.6 mg/kg) for muscle relaxation, and isoflurane (1% end-tidal concentration) to ensure stable anesthesia depth without compromising cerebral perfusion.[27] The anesthesia protocol was the exact same for both groups.

Blood analysis, including pH, PaO2, PaCO2, glucose, hematocrit, and hemoglobin levels, was conducted following intra-arterial access and immediately post-microsphere injection. Mean arterial blood pressure was continuously monitored and maintained at 80-100 mmHg using a 5-French intra-arterial sheath. Intravenous neosynephrine was administered as necessary to manage mean arterial pressure. Central venous pressure was tracked with a central venous catheter, while intracranial pressure monitoring was employed during the acute phase of experimental MCAO. Capnographic ETCO2 levels were maintained at 35-40 mmHg, verified periodically through direct arterial sampling for PaCO2 accuracy. Body temperature was regulated using heating pads, as monitored by a rectal probe, and blood glucose levels were kept below 120 with IV insulin when needed.

Induction of Ischemic Stroke

On the second day, canines underwent endovascular middle cerebral artery occlusion (MCAO) at the M1 segment. This procedure was achieved using embolic occlusion coils at the M1 and carotid terminus, aimed at simulating a hyper-acute ischemic stroke. Two and a half hours post-occlusion, detailed rsfMRI scans were conducted to assess the impact on brain functional connectivity. Occlusions were randomized between the left and right MCA; however, for imaging analyses, all images were flipped so the occluded side was the right hemisphere, as is common practice in lesion studies.[22,30]

Therapeutic Intervention

Prior to the administration of any therapeutic intervention, successful MCAO was confirmed through arteriographic imaging, highlighting the cessation of blood flow in the M1 segment of the MCA. This step ensured the accurate emulation of an ischemic stroke scenario. Pial collateral recruitment was then assessed through contrast-enhanced arteriography. Following this, seven canines in the treatment group received a precise therapeutic regimen, consisting of an intra-arterial infusion of norepinephrine (0.1-1.52 μg/kg/min) to elevate mean arterial pressure by 25-45 mmHg above baseline, alongside a single 20mg dose of Hydralazine. This treatment, initiated 30 minutes post-occlusion, aimed to enhance cerebral perfusion through a combined approach of pressure elevation and vasodilation.

In contrast, the control group underwent standard care, maintaining mean arterial pressure within the physiological range (80-105 mmHg) to serve as a baseline. This controlled approach allowed for the evaluation of NEH treatment's impact on function connectivity and cerebral perfusion.

Pial collateral scores were determined by a board-certified neuroradiologist based on the extent and timing of collateral blood flow in the ischemic territory, using a scoring system where scores greater than 8 indicated robust collateral circulation ("good"), and scores less than or equal to 8 signified inadequate collateral flow ("poor"). This scoring was critical for stratifying the subjects based on their innate cerebral vascular response to ischemia.

rsfMRI Protocol and Analysis

RsfMRI scans were acquired on a 3T MRI scanner (Achieva, Philips), tailored to the specific requirements of rsfMRI to capture the nuances of brain functional connectivity. The imaging protocol utilized a BOLD-sensitive Echo-Planar Imaging (EPI) sequence with TR/TE=1400 ms/20 ms, voxel size of 2.5 mm, and 300 temporal positions.

Before the acquisition, canines were positioned within the scanner to maximize comfort and minimize movement, with padding and restraints used as necessary. The rsfMRI data preprocessing involved several steps to prepare the data for analysis: motion correction

using FSL's (version v6.01)[14-19] MCFLIRT tool, spatial smoothing with a Gaussian kernel of 2.5 mm FWHM to improve the signal-to-noise ratio, and temporal filtering with a high-pass filter (0.01-0.1 Hz) to reduce low-frequency drift and high-frequency physiological noise. Subsequent data analysis employed group-level Independent Component Analysis (ICA) using FSL's MELODIC tool to identify and separate out the different RSNs, including the Primary Visual, Sensorimotor, Higher-order Visual, and Parietal networks. Each RSN was then individually assessed for changes in functional connectivity before and after the therapeutic intervention.[20] Additionally, whole-brain weighted ROI-to-ROI connectivity analysis was conducted with 262 cortical-only ROIs based on a 2020 canine atlas by Johnson et al (this same atlas was used for co-registration of rsfMRI data).[26] Circular connectivity plots (connectograms) were created based on this analysis to adequately visualize pre- versus post-occlusion connectivity differences (Figure 1). Connectograms were created in CONN (Functional connectivity toolbox) in MATLAB (version R2024a).[32]

Statistical Approach

To quantitatively assess the impact of NEH treatment on the functional connectivity within the identified RSNs, a comprehensive statistical analysis was conducted. Initially, individual component maps generated by ICA were compared between pre- and post-intervention scans across both treatment and control groups. This comparison utilized Threshold-Free Cluster Enhancement (TFCE); a technique designed to robustly handle the issue of multiple comparisons across spatially extended statistical maps without the need for arbitrary thresholding.

Family-Wise Error (FWE) correction was applied to adjust for the multiple testing inherent in neuroimaging analyses, ensuring that reported changes in connectivity were not due to chance. Statistical significance was set at a p-value of <0.05 after FWE correction. Additionally, a linear mixed-effects model was implemented to account for within-subject variations over time and between the different RSNs. This model included terms for treatment group, time point (pre- vs. post-intervention), and their interaction, allowing for the examination of how NEH treatment specifically influenced the dynamics of RSN connectivity post-MCAO.

All statistical analyses (paired t-tests) were performed using FSL's Randomise, providing a robust platform for implementing the complex models required to accurately interpret the rsfMRI data. The results from these analyses not only elucidated the direct effects of NEH on brain network connectivity but also provided insights into the broader implications of perfusion augmentation therapy for restoring functional connectivity following acute ischemic stroke. All scripts are available upon request.

Ethical Considerations

All experimental procedures received approval from the Institutional Animal Care and Use Committee (IACUC) at The University of Chicago which is an AAALAC International accredited facility. The study was designed and conducted in strict accordance with the National Institutes of Health guidelines for the humane care and use of laboratory animals, ensuring ethical and responsible research practices.

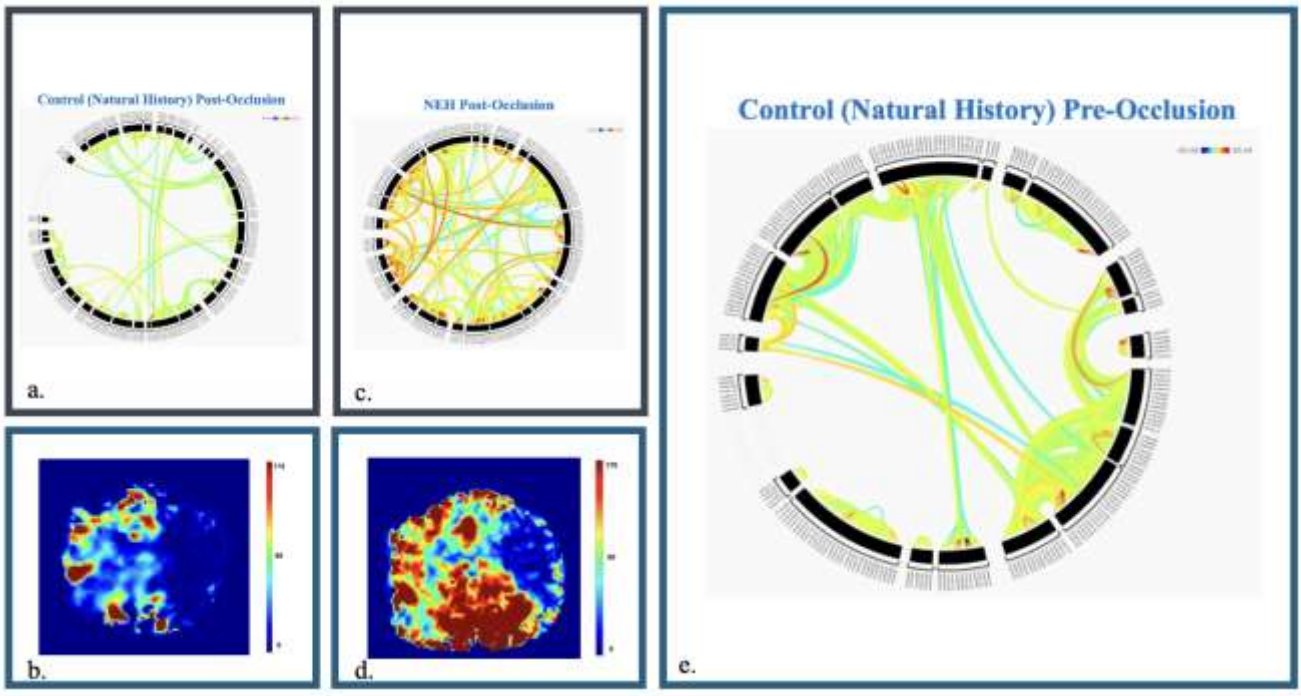

FIG 1. Comparative Analysis of Functional Connectivity and Perfusion in a Canine Model Post-Stroke. Panel (a) illustrates the functional connectivity network in the control group after occlusion, with the thickness and color of the lines indicating the strength of connectivity between regions (atlas-based; Johnson et al 2020)[26]. Panel (b) demonstrates the corresponding loss of perfusion (qCBF measured in ml/100g/min) in the control group, with cooler colors representing reduced blood flow and cell death. Panel (c) displays the functional connectivity network in the NEH-treated group post-occlusion, also reflecting connectivity strength via line color and thickness. Panel (d) shows the NEH group's perfusion, where warmer colors indicate preserved or augmented blood flow relative to the control and the cooler colors in the brain in this case are above the threshold for cell death. Panel (e) depicts the control group's pre-occlusion baseline functional connectivity for comparison. Panels (b) and (d) are quantitative perfusion images (color bar ranging from 0-170 ml/100g/min) that are included (with author permission) for purely demonstrative purposes from an external quantitative perfusion study (Liu et al 2022)[10] to visually correlate the changes in functional connectivity with alterations in perfusion, highlighting the protective effects of NEH on maintaining perfusion after stroke in a single subject.

RESULTS

Utilizing a whole-brain cortical atlas-based ROI-to-ROI analysis, significant global declines in functional connectivity were observed in the control group following occlusion. These changes were captured in the connectograms of Figure 1, depicting a generalized weakening of inter-regional connectivity.

Within specific resting-state networks (RSNs), our analysis revealed a statistically significant decrease in functional connectivity in the Higher-order Visual network (RSN3) post-occlusion in the control group. Conversely, in the NEH-treated group, the Parietal network (RSN4) showed a significant increase in functional connectivity after treatment compared to the pre-occlusion state. This contrast suggests that NEH treatment may confer a protective or restorative effect on the functional integrity of RSNs after stroke (Figure 2). All RSNs identified, including those without significant changes, were anatomically verified by a canine neuroimaging expert, ensuring the reliability of functional connectivity mapping.

Statistical substantiation of these findings was provided by paired t-tests and Threshold-Free Cluster Enhancement (TFCE) with family-wise error (FWE) correction. The meaningful changes in RSN3 and RSN4 surpassed the threshold of TFCE p-corr > 0.95, underscoring the significant impact of occlusion and NEH treatment on these networks. The absence of such significant findings in the Primary Visual (RSN1) and Sensorimotor (RSN2) networks indicates that the effects of stroke and the neuroprotective influence of NEH may be network specific.

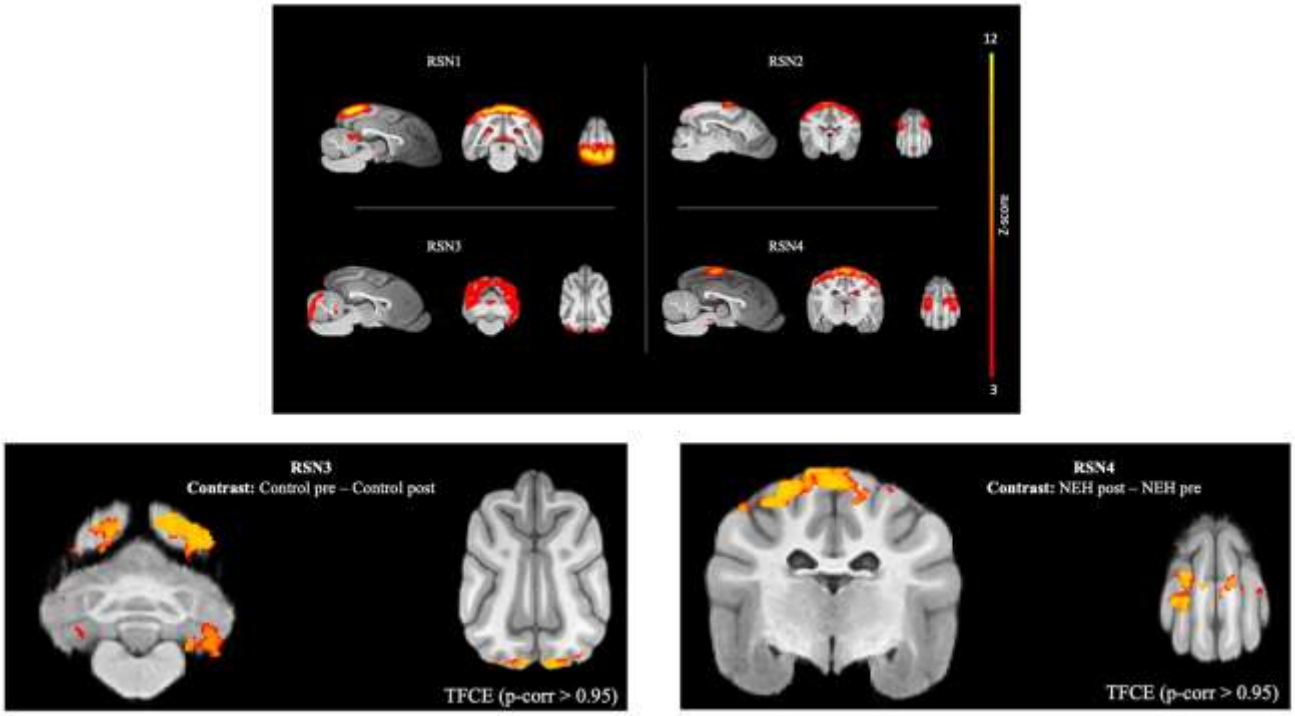

FIG 2. Resting-State Network Connectivity Comparisons Pre- and Post-Occlusion in Control and NEH-Treated Canines. Top row: Baseline functional connectivity within four identified resting-state networks (RSNs) in a canine brain model. From left to right, RSN1 (Primary Visual), RSN2 (Sensorimotor), RSN3 (Higher-order Visual), and RSN4 (Parietal) are displayed, with the intensity of activation indicated by z-score values, where warmer colors represent stronger connectivity. Bottom row: Significant contrasts derived from a paired t-test using FSL's Randomise, indicating changes in functional connectivity within the control and NEH-treated groups. Bottom left (RSN3 contrast: Control pre-occlusion vs. Control post-occlusion) demonstrates a reduction in connectivity post-occlusion within the control group, as evidenced by warmer colors in the pre-occlusion state. Bottom right (RSN4 contrast: NEH post-occlusion vs. NEH pre-occlusion) shows enhanced connectivity post-occlusion in the NEH-treated group compared to pre-occlusion, suggesting an improvement in connectivity within the Parietal network. These contrasts have been thresholded for significance at p-corrected > 0.95 using Threshold-Free Cluster Enhancement (TFCE), highlighting the impact of NEH treatment on RSN connectivity following induced occlusion. All RSNs and statistical maps are overlayed on a canine template atlas (Johnson et al 2020).

DISCUSSION

The present study explored the therapeutic impact of cerebral perfusion augmentation via NEH on functional connectivity alterations in resting-state networks (RSNs) after hyper-acute ischemic stroke in canines. Consistent with our hypothesis, NEH treatment preserved functional connectivity within the Parietal network (RSN4) post-occlusion and, notably, in the Higher-order Visual network (RSN3).[20] This enhancement of connectivity suggests a potential neuroprotective effect, possibly mitigating the typical functional deterioration seen in these networks post-stroke.

Interestingly, while NEH demonstrated beneficial effects in certain RSNs, others like the Primary Visual (RSN1) and Sensorimotor (RSN2) did not exhibit significant changes. This differential response underscores the complexity of cerebral autoregulation post-stroke and highlights the necessity of targeted therapeutic approaches. It further aligns with current perspectives on

the heterogeneity of stroke impacts across different neural circuits, suggesting that therapeutic efficacy may be network-specific, resonating with findings from prior studies on stroke and connectivity.[4, 22-25, 28-32]

Our study suggests that NEH may augment perfusion effectively in specific brain regions, thus preserving or enhancing their functional connectivity. This could have profound implications for stroke recovery, as it supports the premise that pharmacologically maintained perfusion in the acute phase can improve outcomes by preserving network integrity.

However, the intricacies of this relationship must be navigated with caution. While RSN3 and RSN4 showed significant connectivity improvements, suggesting a fortification of network resilience, this effect was not universal across all networks. This finding may be reflective of a complex interplay between the pharmacodynamics of NEH, the inherent resilience of different networks, and the degree of ischemic insult. It compels a deeper investigation into the nuanced ways different RSNs respond to ischemic conditions and the potential for tailored pharmacological intervention.

Considering the limitations, while our canine model offers a translational platform, differences in human and canine cerebrovascular dynamics warrant careful extrapolation of these findings. The sample size, though yielding significant results, constrains the broad applicability of the findings. Future studies with larger cohorts and diverse stroke models could address this limitation and confirm the generalizability of the results.

Implications for patient care are cautiously optimistic. The identification of functional connectivity as a quantifiable measure of therapeutic efficacy could inform the management of stroke patients, potentially leading to individualized treatment protocols. Nonetheless, the translation from canine models to clinical practice must navigate the complexities of human stroke pathology and the variability in patient responses to treatment.

For future research, several trajectories appear promising. Investigating the temporal dynamics of NEH therapy, examining dose-response relationships, and extending the analysis to include a broader range of RSNs could provide deeper insights. Studies might also explore the potential of NEH in combination with established reperfusion therapies like thrombolysis.

CONCLUSIONS

Our findings underscore NEH's role as a proof of concept for cerebral perfusion augmentation therapies in acute ischemic stroke, showing significant preservation of functional connectivity in key RSNs, notably in Higher-order Visual and Parietal networks, within a canine model. This indicates that targeted perfusion augmentation is critical for network integrity preservation. The variability in network response underscores the necessity for tailored therapeutic approaches. These results, alongside the demonstrated utility of functional connectivity as a therapy efficacy biomarker, lay the groundwork for integrating perfusion augmentation strategies into stroke management, particularly benefiting patients with limited collateral circulation. Moving forward, NEH's application in the acute stroke phase opens promising avenues for neuroprotection, meriting further research for clinical translation.

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SUPPLEMENTAL FILES

N/A.