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Brain atrophy in heart failure patients following left ventricular assist device implantation or heart transplantation

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Advanced heart failure is associated with accelerated brain atrophy, largely related to chronic cerebral malperfusion. Both heart transplantation (HT) and left ventricular assist device (LVAD) implantation improve vital organ perfusion, but the comparative effect on brain atrophy remains unclear. Given the MR incompatibility of LVADs, we leveraged serial CT imaging in patients who underwent either HT or LVAD implantation. 58 patients were included in this single-center retrospective cohort (23 LVAD; 35 HT). LVAD patients experienced greater brain atrophy (median: 7.1 mL/year; IQR: 0.9–15.7) than transplant patients (median: 0.4 mL/year; IQR: −6.7–13.9), but this difference was non-significant (p=0.09). Temporal atrophy (expansion of the Sylvian fissure) was greater in LVAD patients (median: 0.91 mm/year; IQR: 0.14–2.27) than HT patients (median: 0.10 mm/year; IQR: 0.02–0.55), p=0.005. These observations reveal a need for future work to prospectively quantify brain atrophy after LVAD implantation and HT, while comparing with that of advanced heart failure.
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Advanced heart failure is associated with accelerated brain atrophy, which is largely attributed to chronic cerebral malperfusion. Brain atrophy is a key contributor to cognitive impairment, and some patterns of brain atrophy in patients with heart failure mimic those of Alzheimer's disease.[1] Both heart transplantation (HT) and left ventricular assist device (LVAD) implantation intend to improve vital organ perfusion, but the comparative impact of each respective treatment on brain atrophy remains unclear. Brain atrophy data in LVAD patients are particularly sparse, in large part because LVADs are MRI incompatible. MR imaging after LVAD explantation has revealed smaller brain volumes as compared to patients with heart failure,[2]

Non-standard abbreviations: LVAD, left ventricular assist device; HT, heart transplantation; MRI, magnetic resonance imaging; CT, computerized tomography

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but explanted patients may be fundamentally different than patients on long-term support. Because destination therapy now accounts for the majority of implants, understanding the cerebral consequences of chronic exposure to LVAD flow dynamics warrants investigation.[3] Fortunately, improvements in computed tomography (CT) resolution facilitate reliable assessment of several metrics of brain volume. Here, we leverage serial CT imaging in advanced heart failure patients who undergo LVAD implantation, and advanced heart failure patients who undergo heart transplantation serve as a comparator group.

This single-institution retrospective cohort study was approved by the Institutional Review Board, and the study conformed to STROBE guidelines for observational studies. Given the retrospective nature of the study, a waiver of consent was granted. Eligible patients were ≥18 years old with advanced heart failure who underwent either HT or continuous-flow LVAD implantation between 2009 and 2021 if they underwent computed tomography (CT) imaging of the head < 3 months preceding *and* > 6 months after intervention (Figure 1). Patients were excluded if they had a diagnosis of ischemic or hemorrhagic stroke in the interval between the two scans. Even in the absence of a clinical diagnosis of stroke, patients were excluded if an interval subclinical infarct was noted on the follow-up CT. LVAD patients were excluded if they underwent HT prior to the second CT scan. All neuroimaging studies were acquired in the axial plane with 5 mm slice thickness. Imaging studies were deidentified and stripped of date and time prior to being uploaded to ITK-snap for segmentation. After setting the window to 40 and level/center to 80, a trained physician manually segmented the cerebral volume (brainstem and cerebellum were not segmented) and lateral ventricular volume from each image slice using a stylus pen and mouse.[4] The ITK-SNAP linear measurement tool was then used to quantify several linear correlates of brain volume (Figure 2). Each 3D mask and linear measurement was reviewed by a second trained physician for validation, and in the case of disagreements, both physicians reviewed the study together to achieve consensus.

Fifty-eight patients met the eligibility criteria (23 LVAD and 35 HT; Figure 1). The median duration between the two imaging studies was 2.0 years (IQR: 1.1–2.8). Baseline characteristics were largely similar between the two groups (Table 1), but chronic kidney disease was more common in HT patients (57% vs 22%, p=0.008). Across the whole cohort, cerebral volume loss occurred at rate of 3.6 mL/year (~0.4% of cerebral volume per year). Figure 3 depicts the rate of cerebral volume loss separately for those treated with HT versus LVAD, and Figure 4 depicts the individual variability. Table 2 reports the statistical comparison for brain atrophy metrics between the two groups. The point estimates raise the possibility of a meaningful difference in cerebral atrophy (LVAD: 7.1 mL/year; HT: 0.4 mL/year), but the difference was not statistically significant (p=0.09). In comparing other metrics of brain atrophy (Table 2), no significant differences were noted between LVAD and HT patients, with the exception of the change in Sylvian fissure diameter, which serves as a measure of temporal lobe atrophy and was larger in LVAD patients (0.91 mm/year vs 0.10 mm/year; p=0.005). A mixed-effects linear model confirmed the findings reported in Table 2 after accounting for age and sex, indicating that HT vs LVAD was only statistically relevant to the change in Sylvian fissure diameter (coefficient for HT was −0.86; 95% CI −1.37 to −0.35; p=0.001).

Three different LVADs were included in this study (HVAD, HM2, HM3), and although each LVAD subgroup was very small, similar rates of cerebral atrophy were observed in each (HVAD: 8.89 mL/year, HM2: 6.72 mL/year, HM3: 6.78 mL/year; p=0.71). The three LVAD subgroups

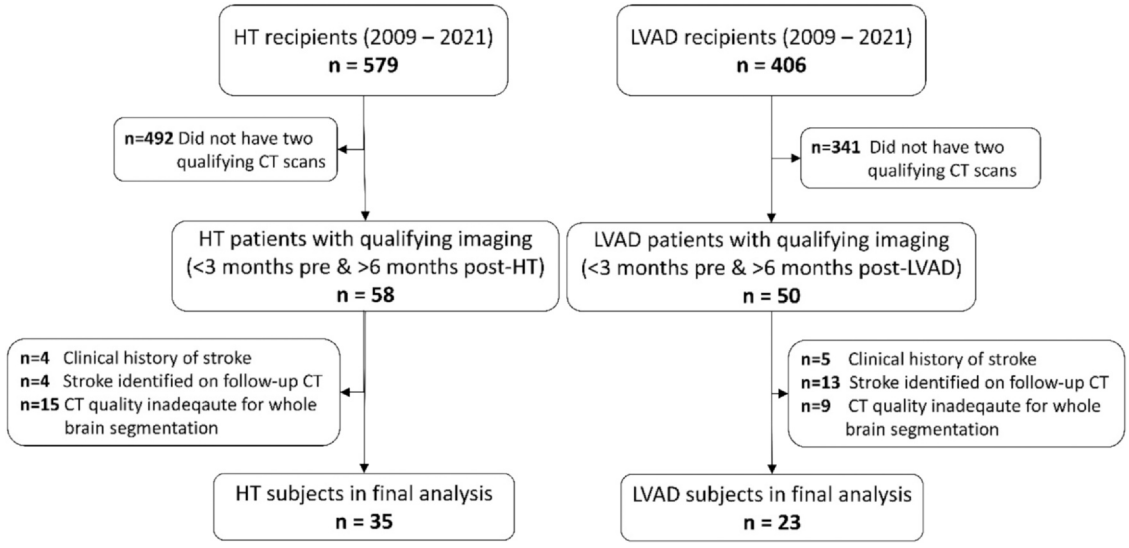

Figure 1 Study enrollment flow diagram: The flow diagram depicts the number of patients with HT and LVAD during the study period, along with reasons for exclusion, arriving at the final cohort of 35 HT patients and 23 LVAD patients. CT quality was deemed to be inadequate for segmentation in the case of imaging artifact (most commonly motion artifact), incomplete brain coverage within the field of view, or otherwise incomplete data.

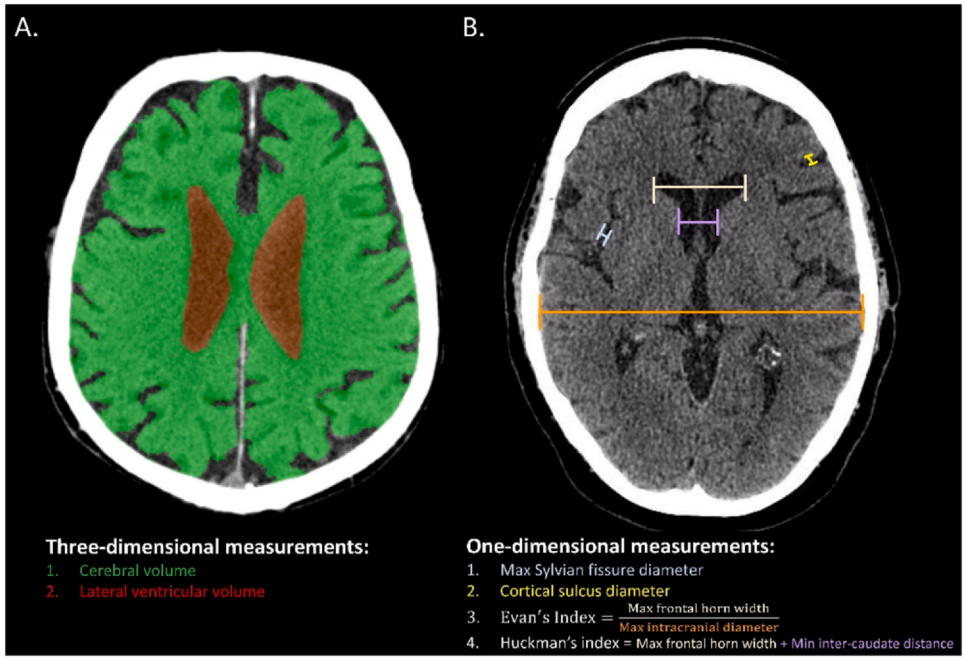

Figure 2 Neuroimaging Volumetrics: CT imaging depicts (A) manual segmentation of cerebral volume (green) and lateral ventricular volume (red), performed in ITK-SNAP. A single axial section is depicted, but the manual segmentation was performed on every section to facilitate a 3-dimensional volumetric analysis. (B) One-dimensional surrogate metrics of brain volume were also assessed in the axial plane. Each metric is indicated by color coded bars and corresponding text below the image.

Table 1 Baseline Characteristics of Patients who Underwent HT or LVAD Implantation

	HT n = 35	LVAD n = 23	p-value
Age, year	55 (46 – 63)	58 (48 – 69)	0.39
Sex, % female	11 (31%)	5 (22%)	0.42
Race, %			0.60
White	22 (63%)	16 (70%)	
Black or African American	13 (37%)	7 (30%)	
LVAD device type			
HeartMate II		11 (48%)	
HeartMate III		9 (39%)	
HVAD		3 (13%)	
Non-ischemic cardiomyopathy, n (%)	26 (74%)	15 (65%)	0.46
Medical history preceding HT/LVAD			
Hypertension	28 (80%)	17 (74%)	0.59
Type–2 diabetes	18 (51%)	10 (43%)	0.55
Hyperlipidemia	20 (57%)	10 (43%)	0.36
Chronic kidney disease	20 (57%)	5 (22%)	0.008
Prior cigarette smoking	14 (40%)	10 (43%)	0.79
Post-op ICU days	8 (4 – 16)	6 (4 – 20)	0.67
Indication for follow-up CT brain			0.22
Altered mental status	12 (34%)	7 (30%)	
Headache	15 (43%)	6 (26%)	
Fall/trauma	2 (6%)	4 (17%)	
Dizziness/presyncope/syncope	5 (14%)	3 (13%)	
Memory loss	1 (3%)	0 (0%)	
Weakness	0 (0%)	2 (9%)	
Screening (to give tPA for device clot)	0 (0%)	1 (4%)	

Continuous variables are reported as median and interquartile range (as opposed to mean and standard deviation because of significant skew). Categorical variables are reported as proportions. P-values were calculated by Wilcoxon-Mann-Whitney test and chi-squared tests, respectively. HT indicates heart transplant. LVAD indicates left ventricular assist device. ICU indicates intensive care unit.

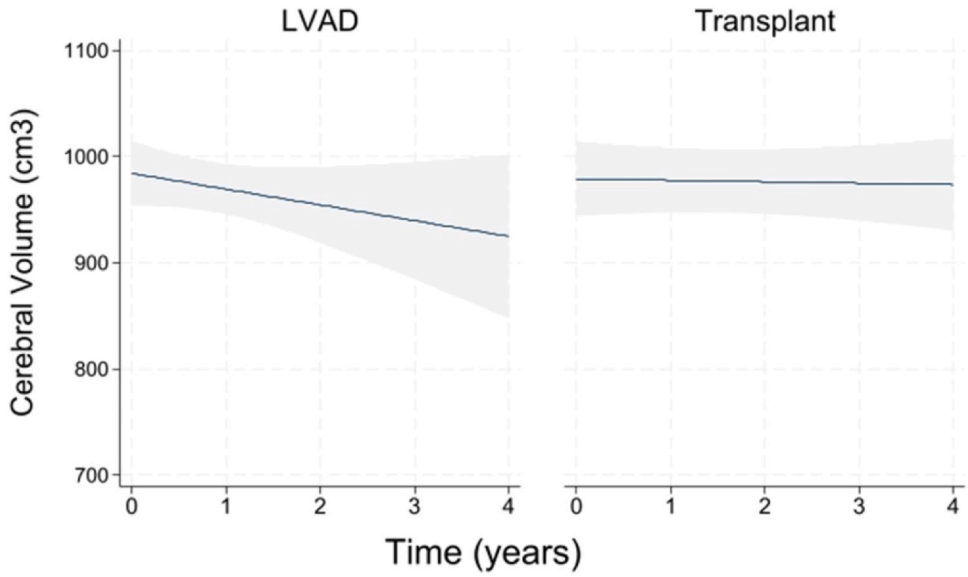

Figure 3 Brain Atrophy after LVAD Implantation or Heart Transplantation: A linear model depicts the change in cerebral volume over time, comparing patients who received LVAD implantation (LEFT) and heart transplantation (RIGHT).

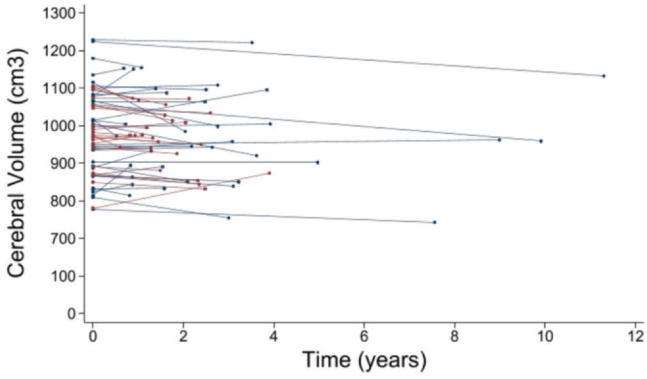

Figure 4 Individual Variability in Cerebral Atrophy: The baseline and follow-up cerebral volumes are depicted for each subject (connected scatterplot). Heart transplant patients are depicted in dark blue. LVAD patients are depicted in maroon.

also demonstrated similar degrees of temporal atrophy (HVAD: 1.15 mm/year, HM2: 0.83 mm/year, HM3: 0.91 mm/year; p=0.64). In a secondary analysis, HVAD and HM2 patients were excluded, so that only HM3 patients could be compared with HT patients to best reflect current practice (Table S1). These secondary results mirrored the above described primary analysis. More specifically, greater temporal atrophy was observed in HM3-LVAD patients as compared to HT patients (median 0.91 mm/year vs 0.10 mm, respectively; p=0.02), and point estimates raise the possibility of a clinically relevant, though not statistically significant, difference in cerebral atrophy (0.68 mL/year vs 0.40 mL/year, p=0.43).

This retrospective cohort provides preliminary evidence that heart failure patients who undergo LVAD implantation experience greater brain atrophy, in particular temporal lobe atrophy, than those who undergo HT. However, power was limited by the small sample size and limited time between baseline and follow-up imaging. The rate of cerebral atrophy reported here was approximately 0.4%/year across the entire cohort (0.8% for LVAD patients and 0.1% for HT patients). For reference, brain atrophy is estimated to be < 0.2% per year in a broadly inclusive population of adults between 30 and 60 years of age,[5] in contrast to 0.3%–0.4%/year in patient with heart failure.[6] More dramatic atrophy is observed in older patients, and in particular older patients with Alzheimer's disease, where it exceeds 1%/year.[7] However, caution is warranted in comparing the current results with previously reported rates of atrophy which were derived from MRI data. Here, we rely on CT imaging because LVADs are MR

Table 2 Comparing Metrics of Brain Atrophy Between HT and LVAD

	HT n = 35	LVAD n = 23	p-value
Cerebral volume loss (mL/year)	0.4 (–6.7, 13.9)	7.1 (0.9, 15.7)	0.09
Increase in lateral ventricular volume (mL/year)	0.47 (–0.10, 3.31)	1.26 (–0.18, 2.91)	0.53
Increase in cortical sulcus diameter (mm/year)	0.05 (–0.01, 0.19)	0.05 (–0.69, 0.86)	0.67
Increase in Sylvian fissure diameter (mm/year)	0.10 (0.02, 0.55)	0.91 (0.14, 2.27)	0.005
Increase in Huckman's index (per year)	0.51 (–1.66, 2.16)	0.29 (–.47, 1.86)	0.71
Increase in Evan's index (per year)	0.001 (–0.002, 0.007)	0.002 (–0.002, 0.007)	0.92

Values were reported as medians and interquartile ranges. Each measure of atrophy was calculated as the change in the brain volume metric per year. Reported p-values were calculated by Wilcoxon-Mann Whitney tests.

incompatible, and although atrophy may be similar on MRI and CT,[8] extrapolation should be done cautiously. More importantly, the referenced rate of brain atrophy in heart failure patients (0.3–0.4%/year) was not inclusive of patients with severe heart failure. Because malperfusion is a key mechanism underpinning brain atrophy in heart failure, this is likely an underestimate of the degree of atrophy that might be observed in advanced heart failure. Still, the results of the current study raise the distinct possibility that hear failure associated brain atrophy is ameliorated by heart transplantation more so than LVAD implantation. Whether the observed rate of atrophy in LVAD patients is similar, smaller, or larger than advanced heart failure requires further investigation, as do the mechanism of brain atrophy after LVAD implantation. LVAD implantation improves end-organ perfusion, but brain perfusion may still be suboptimal, particularly in the context of right heart failure, because elevated central venous pressure increases intracranial pressure, which in turn reduces cerebral perfusion pressure.[9] More unique to LVAD physiology, we also propose that brain atrophy in LVAD patients may be, in part, related to the unique flow pattern of the pump. Despite improvements in absolute flow, cerebral autoregulation may partially improve but fail to normalize after LVAD implantation,[10,11] Abnormal CBF pulsatility is expected after LVAD implantation,[12] which may precipitate cerebral microvascular remodeling that contributes to volume loss and cognitive impairment.[13,14] Indeed LVAD-associated cerebral microvascular injury has been observed at autopsy,[15] but ultimately these mechanisms require further investigation and may reveal opportunities to optimize LVAD management.

Change in whole brain or cerebral volume provides the most intuitive metric of atrophy, but CT imaging may provide limited sensitivity for small changes that occur over short intervals. Similarly, the immediate post-operative brain volume may be confounded by the intervention (i.e., improved perfusion may transiently increase brain volume, or peri-operative ischemic insults may transiently increase the rate of atrophy). Because brain atrophy may not respect a linear function around that the time of intervention, we only included imaging obtained >6 months post-HT/LVAD. To better characterize the trajectory of brain volume in future prospective work, multiple post-operative time-points may be needed. Lateral ventricular volume is a commonly used surrogate of brain atrophy, but is preferentially sensitive to atrophy of deep brain structures.[16] The validated 1-dimensional metrics reported here provide additional regional characterization.[17] For example, Sylvian fissure diameter reflects medial temporal lobe atrophy[18] and was the only metric that revealed a statistically significant difference between the two groups. In advanced heart failure patients, temporal atrophy has been associated with cognitive impairment.[19] The ideal assessment of atrophy remains unclear in this unique patient population, so using several metrics to characterize different regional aspects of brain atrophy may be reasonable. In future work, subregions susceptible to hypoxic/ischemic injury could be segmented. Further, cerebellar atrophy was not quantified here but may be considered in future work, given its potential relevance to cognition.[20]

This study has several limitations. The small sample size limits the ability to detect potentially clinically meaningful differences, and the single-center design limits generalizability. The retrospective nature of the study introduces selection bias because only a minority of HT and LVAD patients had qualifying imaging. The indications for CT imaging were reassuring, but those who underwent imaging may not be representative of the broader population (i.e., those getting scanned for headaches or altered mental status may represents less healthy subgroup). Despite the similar baseline characteristics, there are likely unmeasured differences that may confound group comparisons. To resolve some of these limitations, a prospective cohort is needed in which all patients undergo study specific neuroimaging at predefined intervals. LVAD patients were non-significantly older, and age is a key factor when considering brain atrophy.[21] Thus, age was included in the mixed-effects model, which reassuringly confirmed the observed difference in temporal atrophy. A larger cohort will allow more potentially confounding variables to be included in the model. CT imaging was used in this study out of necessity (LVADs are not MR compatible), but it provides less spatial resolution than MRI and thus less volumetric precision. CT is therefore expected to be less sensitive to small changes/differences. Simply contrasting LVAD and HT is likely an oversimplification given the diversity in both groups. With a larger cohort, it may be interesting to consider the relevance of cardiac function metrics in both groups. Similarly, three different LVADs were used during the study period, and although atrophy was similar between these device subgroups and the HM3 subgroup yielded similar results to the overall cohort, a future larger study should focus on HM3 patients in order to reflect current practice. There is substantial individual variability with respect to brain atrophy, but a larger cohort will be needed to have sufficient power to recognize associations between brain atrophy and clinical factors (i.e., cardiopulmonary variables). Ultimately, these limitations should temper conclusions drawn here which should be interpreted as hypothesis generating rather than practice altering.

This pilot study provides evidence that brain atrophy associated with heart failure may be attenuated by HT more so than LVAD implantation. Thus, greater rates of atrophy, in particular temporal lobe atrophy, were observed in LVAD patients than HT patients. This reveals a need for future work to prospectively and systematically quantify brain atrophy in patients with advanced heart failure and after either LVAD implantation or HT. Preclinical models may be best positioned to explore potential mechanisms underlying brain atrophy after LVAD implantation.

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Disclosures

Dr. Genuardi reports consulting income from Respicardia and a research agreement with Abbott. The other authors report no conflicts.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Christopher G. Favilla reports financial support was provided by National Institutes of Health. Christopher G. Favilla & Michael V. Genuardi reports financial support was provided by National Center for Advancing Translational Sciences. Michael V. Genuardi reports a relationship with ZOLL Respicardia Inc that includes: consulting or advisory. Michael V. Genuardi reports a relationship with Abbott Cardiovascular that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplemental data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2025.100211.

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