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Original Research

Neuroradiology

White Matter Changes in Comatose Survivors of Anoxie Ischemic Encephalopathy and Traumatic Brain Injury: Comparative Diffusion-Tensor Imaging Study

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Cardiac arrest and traumatic brain injury (TBI) **may** lead to similar clinical presentations that include prolonged impaired consciousness, even though these two types of insult have vastly different pathophysiologic mechanisms. These differences are reflected in the spatial distribution of abnormalities over the brain. In TBI, shearing and acceleration-deceleration forces lead to diffuse axonal injury mosHy in the central structures such as the brainstem and corpus callosum, often associated with contusions in the cerebral hemispheres *(1).* In cardlac arrest. the areas most vulnerable to damage are the watershed areas of the cerebral hemispheres (f_ .

Diffusion-tensor (DI) imaging providsinformation not only on lesion localization but also on the nature of white malter damage. The DT imaging parameter axial diffusivity (Ai) depends chiefly on the diffusibility of water molecules parallel to a tract, whereas radial diffusivity (AJ.) assesses water diffusion perpendlcular to the tract(§). Thus, changes in >.1 are thought to be associated prlmarlly wlth axonal damage, whlle changes In J...1 are thought to relate to myelln Injury (Il.-Il). These parame ters provlde greater anatomie and functional information !han scalar DT imaging parameters such as fractional anisotropy and the apparent diffusion coefficient (!l.,!1.-U) , whi ch havebeen more extensively evaluated !han >. 1 and J..J.. These constru cts have been validated in animal models (!l.-Il.,H ,1.§). Their meaning in humans has been less studied.

We hypothesized that the different pathophysiologic events occurring in the subacute phase alter cardiac arrest and TBI have different effects on >.1 and AJ.· The purpose ofthis study was to analyze the anatomie distribution of white malter pathologie abnormalities by using DT imaging in a multicenter prospective cohort of patients with impaired consciousness following cardiac arrestorTBI.

Materials and Methods

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The insti tutional review boards of the participating institutions approved this prospectivestudy. Ali patients' next of kin and healthy control subjects gave informed consent. The patients and healthy control subjects were recruited during a study on the relevance of DT imagIng blomarkers In the predlctlon of recovery of consclousness In patients after cardlac arrest and after TBI. In that study, the researchers used the same inclusion and exclusion criteria, the same clinicat data and the same methods ofmagnetic resonance

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(MR) imaging acquisition and MR imaging analysis as were used in the present study. The study on the relevance of DT imaging biomarkers in the prediction of recovery of consciousness led to lwo articles. one for cardiac arrest (.1fil and the other for TBI (1Z). and the design ls reported in more detail in those lwo previous articles (1§,ffi . Two authors (V.P., a computer scientist with 1O years of experience, and D.G., a neuroradiologist with 15 years of experience) processed the DT imaging acquisitions. They had no access to the clinical information and outcome of the patients.

Patients

Consecutive patients were enrolled prospectively in eight intensive care units in Paris, Lille, Lyon, Montpellier, Nancy, Rouen, and Bordeaux in France and in Liège in Belgium following cardiac arrest or TBI between October 2006 and February 201O. Patients were eligible if they *(a)* were between 18 and 85 years old, and *(b)* had severe brain damage, as expressed by *(i)* inability to follow simple commands 7-28 days afler the incident, unexplained by sedation, and *(ii)* a Glasgow Outcome Scale (1fil score of 1 or 2 at 12 months afler the injury or a Glasgow Outcome Scale score of 3 that was explained by cognitive and not purely physical impairment. On the basis of these inclusion criteria, 57 patients with cardiac arrest and 55 patients with TBI were eligible. Patients were excluded if lhey *(a)* had a central neurologie disease prior to cardiac arrest or TBI (n = 2); *(b)* had a penetrating head injury (n = 1); *(c)* were moribund (expected survival of< 24 hours) (n = O); *(d)* had a contraindication to MR imaging *(n* = 4); or *(e)* were too unstable to be transported and to undergo MR lmaglng *(n* = 0). On the basls ofthelr ellglblllty, we enrolled 54 patients wlth cardlac arrest and 51 patients with TBI. Ofthese, the MR imaging data in five patients with cardiac arrest and in 11 patients with TBI could not be evaluated because of a suboptimal MR imaging acquisition, as a result of motion (four cardiac arrest patients, five TBI patients), other artifacts (zero cardiac arrest patients, one TBI patient), or deviation in the MR imaging protocol (one cardiac arrest patient, one TBI patient), or because an insufficient number of heallhy control subjects were imaged (zero cardiac arrest patients, four TBI patients). Finally, we included 49 of 57 patients wilh cardiac arrest (86%) and 40 of 55 patients with TBI (73%) with sufficient quality normalized DT imaging data. Demographic and clinical characteristics of the patients are summarized in Table 1.

Table 1. Demographics and Clinical Characteristics of the Patients

Cardiac Arrest

The cause of the cardlac arrest was prlmarlly cardlac (cardlacarrest orlglnatlng ln the heart [eg, myocardlal lnfarctlon)) ln 39 of 49 patients (80%) and secondarily cardiac (cardiac arrest resulting !rom disease outside the heart [eg, severe hypoxia or hyperkalemia)) in 10 of 49 patients (20%). The mean duration of no flow before cardiopulmonary resuscitation was 5 minutes (interquartile range, 0-tO minutes). lltook a median 0120 minutes (interquartile range, 10-36 minutes) for the circulation to become fully effective under cardiopulmonary resuscitation. Hypothermia was induced in 29 of 49 patients (59%). Al admission, the mean serum troponin I level was 0.48 ng/ml (0.48 µg/L), with an interquartile range of0 .1- 4.4ng/ml (0.1-4.4 µg/L).

Traumatlc Brain Injury

TBI was caused by a motor vehlcle accident ln 26 of 40 cases (65%) (20 drivers or passengers [50%) and six pedestrians(15%1), by a fall in nine of 40 cases (23%), and by another mechanism in five of 40 cases (13%). On a computed tomography (CT) scan obtained within 48 hours of the TBI, six of 40 TBI patients (15%) had an epidural hematoma, 14 of40 patients (35%) had a subdural hematoma, 34 of 40 patients (85%) had a subarachnoid hemorrhage, 27 of 40 patients (68%) had one or more contusions, and nine of40 patients (23%) had a midline shifllarger than 6 mm. None of the TBI patients had signs of ischemia on this early CT scan. Of 40 patients, 18 (45%) had a Marshall classification diffuse injury 1-11, five (13%) had a Marshall classification diffuse injury 111, one (3%) had a Marshall classification diffuse injury *IV,* and 15 (38%) had a mass lesion (eight patients had **an** evacuated mass lesion and seven patients had a nonevacuated mass lesion) (1i). Fourteen of 40 TBI patients (35%) underwent a neurosurgical intervention.

Heallhy Control **Subjects**

To contrai for multisite variability in DT imaging data, in each center we compared the patients' DT imaging values with those of a total of 111 healthy volunteers, wilh four to 51 control subjects per center; 60 of 111 (54%) were men and 51 (46%) were women (mean age, 33 years ± 3 [standard deviation)). These contrai subJects underwent MR lmaglng wlth the same acquisition parameters as the patients. Volunteers were recruited by the local principal investigator among staff members of each center. They gave written informed consenlto study participation. Individuals with no history of neurologie disease requiring medical attention were eligible. We excluded volunteers with abnormalities in the morphologie sequences, as occurred in lwo individuals (lwo of 113, 2%): one with mild atrophy and another with asymptomatic white matter disease.

Clinicat **Data** Co.,ction

Data were prospectlvely collected by using standardized case report forms and a Web-based, encrypted, and centrally managed data management system. Specllfic data Included the followlng: patient demographlcs; Initial cllnlcal status and cranlal CT scan; and 1-year outcome, including the Glasgow Outcome Scale score on a five-point scale (1fil and cognitive and physical impairment as assessed by the investigating team al each participating center via a telephone interview or via an in-persan visit. A central study monitor verified all data for accuracy, consistency, and completeness.

MR Imaging Acquisition

MR imaging was performed afler enrollment and as soon as MR imaging was clinically feasible, which was a mean of 23.2 days ± 1.7 (range, 7-57 days) afler TBI and a mean of 13.1 days ± 1.2 (range, *5-47* days) afler cardiac arrest. Vital signs were continuously monitored during imaging. Sedation, if any, was maintained. MR imaging was performed in eight centers using nine imaging units from three manufacturers (Siemens [Erlangen, Germany], GE Healthcare [Milwaukee, Wis], and Philips Healthcare [Eindhoven, the Netherlands)) and included units with both 1.5- and 3.0-T magnetic field strength. The imaging protocol has been described in previous publications (1§.,ffi . The DT imaging acquisition parameters were optimized for each MR unit, wilh minimal specifications of a pixel size of at most 3 x 3 x 3 mm, a *B* value of 1000 mT/m, and al leasl 12 gradient directions. The clinical team did not have access to the DT imaging results, whlle the investigators processing the DTI maging acquisitions 0f.P. and D.G.) had no access to the clinical information and outcome of the patients. No adverse events related to MR imaging were reported.

MR Imaglng Analysls

The pre- and postprocessing of the DT imaging data are described in Appendjx E1 (online). This process uses nonlinear registration of À1 and À⊥ maps into a standard space. as implemented in software (FLIRTIFNIRT procedures; FSL Software Technologies. New Delhi, India). The averaged À1 and À⊥ values were then extracted in 19 predefined white malter regions of interest(ROIs) (Bg_l), which were selected from the white malter allas (. To account for intercenter and intersequence variabili\y, these values were normalized to values of healthy contrai subjects by scaling each value of a patient to the mean of the corresponding parameter calculated !rom the healthy contrai subjects who underwent imaging by using the same acquisition parameters in the same center, as previously described ®,II). We tested the effects ofthree factors (acquisition/center, ROIs, groups) on the mean of the regional fractlonal anlsotropy calculated in the patients and contrai subjects by uslng a three-way analysis of variance. The results showed that, before normalization, the three factors were significant (P < .05), and aller normalization, only the group effect significantly explained the data variabili\y. We did not adjust for the center-specific standard deviation. The intrasite coefficient of variation (ratio of the standard deviation and the mean) ranged !rom 2% (within the splenium of the corpus callosum) to 10% (within the body of the corpus callosum) with homogeneous variance across centers (BarUett test). For explorative analyses, the 19 ROIs were gathered into flve groups: lower brainstem region, cerebral peduncles reglon, corpus callosum reglon, right hemisphere, and left hemisphere Œi9.1). The statistical analyses ofraw MR data were performed by a computer scientist(V.P., with 10 years of experience) and a mathematician (H.B., with 30 years of experience). Image analysis and quali\y contrai of MR images were performed by two neuroradiologists(D.G., with 15 years of experience, and E.T., with 10 years of experience).Data consistency and data integrily were checked by an anesthesiologist(L.P., with 20 years of experience).

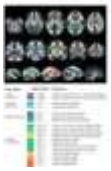

Figure 1:. Automatically segmented white malter ROIs for measurement of DT imaglng parameters. The background images are the FMRIB58-fractional anisotropy standard space images provided in FSL. The ROIs defined by Mort et al (W are color coded and superimposed on these background fractional anisotropy images. For explorative analyses, the color-coded ROIs in the anterior and posterior brainstemwere collapsed into a single lower brainstem region; the ROIs in the cerebral peduncles were collapsed into a single cerebral peduncles region; the ROIs in the genu, splenium, and body of the corpus callosum were collapsed into a single corpus callosum region; and the ROIs in the paired anterior and posterior limbs of the internai capsule, sagittal stratum, superior longitudinal fasciculus, externalcapsule, and corona radiata were collapsed into right hemisphere and leflhemisphere regions.

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Statistical Analysis

Data were analyzed by using statistical software (StatView 5.0, SAS Institute, Cary, NC; and SPSS 18, SPSS, Chicago, Ill). Values are expressed as means and standard errors of the mean unless otherwise stated. Differences in demographic and clinical variables were tested by uslng the Student /test and the ***,j-*** test, as approprtate. DT Imaglng variables had normal distribution (according to the Kolmogorov-Smirnov test); therefore, we used parametric tests. We used the method of general linear modeling (analysis of variance with Bonferroni post hoc) for within- and between-group comparison of DT imaging variables in healthy contrai subjects, TBIpatients, and cardiac arrest patients. Multivariate analyses were performed to evaluate the results afler adjustment for age and sex. The interaction between variables was also assessed. We calculated Pearson correlation coefficients between the DT imaging parameters in each left-sided ROI and the correspondingright-sided ROI. *P* values were corrected for multiple testing by multiplication of the *P* values by the number oftested hypotheses; for example, *P* values were mulliplied by 19 when we compared DT Imaglng values among the groups In the 19 ROIs (Bonferronl method). Throughout the article, we present the corrected *P* values. A difference with a corrected value of $P < .05$ was considered significant.

Results

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The À1 and À⊥ values in various brain regions of patients and healthy contrai subjects are illustrated in Figures 2- g .

Figure 2:. Normalized values of À1 and À.c in the lower brainstem region of patientsand healthy contrai subjects. Box plots show the median (middle horizontal line in each box), interquartile range (25th [bottom of box) to 75th [top of box] quartiles), and the minimum (bottom ofwhisker) and maximum (top ofwhisker) values. Asterisks = Pvalues forwithin- and between-groupcomparisons. When the combinedROIs were compared, P values wilh significant differences were as follows: For À1, TBI versus cardiac arrest patients, $P < .01$; for À1 and À⊥ TBI versus healthy contrai subjects and cardiac arrest patients versus healthy contrai subjects, $P < .01$. There were no significant interactions between the anterior and posterior brainstem. • = $P < .05$, •• = $P < .01$, NS = not significant.

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Figure 3:. Normalized values of À1 and À.1 in the cerebral peduncles region of patients and healthy contrai subjects. Box plots show the median (middle horizontal line in each box), interquartile range (25th [bottom of box) to 75th [top of box] quartiles), and the minimum (bottom of whisker) and maximum (top ofwhisker) values. Asterisks = Pvalues forwithin- and between-group comparisons When the combined ROIs were compared, *P* values with significant differences were as follows: For À.c, TBI versus cardiac arrest patients, $P < .01$; for À1 and À.1, TBIpatients versus healthy contrai subjects and cardiac arrest patients versus healthy contrai subjects, $P < .01$. There were no significant interactionsbetween the left and the right cerebral peduncles. •• = $P < .01$, NS = not significant.

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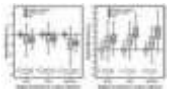

Figure 4:. Normalized values of A1 and A.Lin the corpus callosum region of patients afterTBI, of patients alter cardiac arrest, and of healthy contrai subjects. Box plots show the median (middle horizontal line in each box), interquartile range (25th [bottom of box] to 75th [top ofbox] quartiles), and the minimum (bottom ofwhisker) and maximum (top ofwhisker) values. Asterisks = Pvalues for within- and between-graup comparisons. Vl/hen the combined ROIs were compared, *P* values with significant differences were as follows: For A.L, TBI versus cardiac arrest patients, *P* < .01; for A_1 and A1., TBI patient versus healthy contrai subjects and cardiac arrest patients versus healthy control subjects, *P*< .D1. For interaction between the splenium, body, and genu for A_1 , *P* < .05, and for A1., *P* < .01. •• = *P* < .01. NS = not significant.

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Figure 5:. Normalized values of A_1 and A.L in the cerebral hemispheres of patients and healthy control subjects. The rlght hemlsphere ls at lefl, and the left hemlsphere ls at rlght. Asterlsks = *P* values forwithin- and between-group comparisons. Symbols in each line = mean for each member of the graup indicated; errar bars= standard errors of the mean. For interaction between the ROIs in the right hemisphere for both A_1 and A_J. *P* < .01; for interaction between the ROIs in the leflhemisphere for A_1, *P* < .01. Notice the symmetrical pattern of involvement for A_1 in TBI and cardiac arrest patients and for A_J in cardiac arrest patients, while the pattern of involvement for A.L in TBI patients is asymmetric. • = *P* < .05,•• = *P* < .01, *ALIC* = anterior limb of internai capsule, *CA*= cardiac arresl, *CR*= corana radiata, *Clrf* = heallhy contrai subjecl, *EC* = external capsule, *NS* = no! significant, *PLIC* = posterior limb of internai capsule, *SLF*= superior longitudinal fasciculus, SS= sagittal stratum.

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A1 and A_J in **Patients versus** Healthy Control **Subjects**

The A_1 and A_J in the anterior braInstem and A_J In the posterlor braInstem were hlgher in cardiac arrest patients than in control subjects (all ***P***< .01). The $>_1$ was lower In the postertor braInstem, and À1. **was** hl gher In the posterlor braInstemand In the antertor brainstem in TBIpatients compared with contrai subjects (all *P* < .01) (Ei.9.I). The 11_1 was lower (P < .05) and 111. was higher (P < .05) in TBI patients and cardiac arrest patients !han in contrai subjects in the left and right cerebral peduncles, body, genu, and splenium of the corpus callosum (except for11_1 in the genu) (Figs 3,1). Thus, in central white malter, A_1 differed li'om that in contrai subjects in six ofseven TBI ROIs and five of seven cardiac arrest ROIs (all *P* < .01). The A1.differed li'om that in control subjects in all ROIsin both patient graups *(P* < .01) (Fias 2--1). For the various ROIs in the cerebral hemispheres, Figure 5 shows the comparison of 11_1 and A.Lin patients versus in contrai subjects. Thus, in hemispheres, $>_1$ was decreased compared wilh lhat in contrai subjects in three of 12 TBI ROIs *(P* < .05) and nine of 12 cardiac arrest ROIs *(P*< .01). The 111. was increasedin all TBI ROIs (P < .01) and in seven of 12 cardiac arrest ROIs *(P*< .05). Cerebral hemisphere $>_1$ was lower in cardiac arrestthan in TBI in six of 12 ROIs (P< .01), while A.L was higher in TBIlhan in cardiac arrest in eightof 12 ROIS (P< .01).

A1 and A_J in Cardiac Arrest versus TBI Patients

The major flndlngs for the difference ln A_1 and A_J between TBI and cardiac arrest patients are reported in Figures 2- 5. Table 2 presents the type and distribution of abnorrnallties ln central reglons (anterlor and posterlor braInstem, left and rlght cerebral peduncles, genu. body, and splenium of the corpus callosum) and in cerebral hemispheric regions (left and right sagittal strata, superior longitudinal fasciculus, anterior and posterior limb of internai capsule, external capsule, and corana radiata). In both central regions and cerebral hemispheres, A.L was higher (P < .05) in TBI patients than in cardiac arrest patients. In cerebral hemispheres, A_1 was lower *(P* < .05) in cardiac arrest patients than in TBI patients.

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Table 2. Types and Distributionof Abnorrnalities in TBI and CardiacArrest Patients

The differences presented in Figures 2--4 remained significant afler adjustrnent for age and sex.

A1 and A.L In the Left versus the Righi Cerebral Hemlsphere

fi.wdre..§. shows a symmetrical pattern of DT imaging changes in the ROIs in the corresponding right and left hemispheres in patients with cardiac arrest and in contrai subjects. Indeed, there was a significant intercorrelation between DT imaging values of the ROIs in the corresponding right and left hemispheres in cardiac arrest patients (ranging li'om *r*= 0.81 in the extemal capsule to *r*= 0.99 in the corana radiata for A1 and fram *r*= 0.73 in the external capsule to *r*= 0.99 in the corana radiata for A1.: P < .001) and in contrai subjects (ranging li'om *r*= 0.73 in the sagittal stratum to *r*= 0.84 in the anterior limb of the internai capsule for A1 an d li'om *r*= 0.75 in the external capsule to *r* = 0.93 in the corana radiata for À.L; *P*< .001; values close to one represent symmetry between DT imaging values in the ROIs in the corresponding lefland right hemispheres). In TBIpatients, this symmetrical pattern of DT imagina changes was not seen for most ROIs (.

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Table 3. Intercorrelationsbetween DT Imaging Values in Corresponding ROIs in the Left and Righi Hemispheres

Discussion

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This article shows that DT imaging can help distinguish the diflerent pathophysiologicmechanisms that underly similar states of impaired consciousness following TBI and cardiac arrest.

Our main findings are a marked decrease in λ_1 in cardiac arrest patients and a marked increase in λ_1 in TBI patients. These findings are consistent with reported pathophysiologicconcepts, a tact that supports the validity of DT imaging to help distinguish axonal and myelin damage in vivo in groups of patients. Thus, in cardiac arrest, the marked decrease in λ_1 is consistentwithprimaryaxonal damage *(§..1Q-11)* related to energy depletion!rom anoxie ischemia. Primary axonal damage induces changes in the ftuid microenvironment of the central nervous system, to which in turn myelin is susceptible (Z.1-W. The moderate λ_1 increases in our cardiac arrest patients are consistentwithsuch secondary myelin damage@. Conversely, the marked λ_1 increase in many areas o!TBI patients suggests myelin damage, edema, and/or macrophage infiltration as the primary injury. The mechanical forces exerted on the brain in TBI probably cause more myelin damage !han axonal damage. The smaller λ_1 decrease in TBI patients is consistent with axonal damage, caused either by direct trauma (axonotrnesis) or by indirect ischemic damage secondary to extracranial traumatic injuries. In a later phase, brain swelling and increased intracranial pressure may rurther contribute to the axonal damage. In cardlac arrest, there ls a gradient ofInJury severity from the cerebral hemlspheres toward the medulla oblongata, with relative sparing of the central brain structures (ffil. The vascular anatomy in the cerebral hemispheres, characterized by widespread linear arterioles with few anastomoses, increases the vulnerability of the hemispheric white matter to hypoxic-ischemic injury GIT- - Conversely, in TBI patients, A.1 was highly abnormal in bath the central brain structures and the cerebral hemispheres. This finding is consistentwilh the distribution of diffuse axonal injury observed in the classic monkey model of axial trauma caused by rotational and acceleration-<leceleration shearing forces QQ). The λ_1 increase and, to a lesser extent, the λ_1 decrease were asymmetric, being more pronounced in the left cerebral hemisphere of our TBI patients. This predominance of left-sided abnormalities in TBI patients with poor clinical outcomes was expected, as left-sided lesions are more frequenijy symptomatic. The asymmetry was altributable to a left predominance of λ_1 abnormalities and, to a lesser extent, λ_1 abnormali ties, suggesting greater asymmetry of edema and/or myelin damage than of axonal damage. This finding supports the hypothesis that edema and myelin damage are chiefty related to the mechanical trauma, which is an asymmetric assault, whereas axonal damage may be a combined affect of symmetric systemic processes and asymmetric local processes.

Our finding ofgreater λ_1 as compared wilh λ_1 atterations in TBI patients is consistentwith DT imaging findings in the key experimental mouse model of brain injury by MacDonald et al (1Q). The researchers in all previous descriptive DT imagingstudies in humans al the earty subacute phase o!TBI evaluated a later or longer time window than we did in our study GI.1- . included patients with milder brain injury @,,;II- . and/or did no! specify separate diffusivity parameters in various ROIs @. .;II.;II,.2I!). As intuitively expected, λ_1 values and therefore myelin damage played a larger role than λ_1 in a recent DT imaging-based and clinically based prognosUc model in severe TBI (11). To our knowledge, no previous descriptive DT imaging studies in human cardiac arrest patients have been published.

To our knowledge, investigators in only one previous study have compared the use of DT imaging in cardiac arrest patients versus TBIpatients. Our finding of greater severity of central brain structure injury in TBIpatients versus cardiac arrest patients is consistent wilh the findings in the comparative study al a later postinjury phase of Newcombe et al - Although an overall λ_1 decrease was our main finding in cardiac arrest patients, λ_1 in the lower brainstem and cerebral peduncles regions showed larger decreases in TBI than in cardiac arrest. Similarty, in a study of 30 patients with severe TBI evaluated 8 weeks after trauma, λ_1 was decreased and λ_1 was increased in the deep brain regions and brainstem Q.1,il) . \Mlereas we found large differen ces in the cerebral hemispheres between cardiac arrest and TBI, Newcombe et al found broadly simllar DTImaging abnorrnalities In TBI and ischemic-hypoxic brain injury. This discrepancy is ascribable to diflerences in patient populations and MR imaging timing, as well as to the relatively small number of patients studied by Newcombe et al.

Our sludy had several limitations. As was inevitable with a multicenter design , the DTimaging data were acquired wilh different MR imaging machines. We corrected for this source of variability by normalizing the patient values to values in healthy control subjects who underwent imaging with the same parameters on the same machine. Because of the epidemiology ofTBI and cardiac arrest, our TBI patients were younger and cardiac arrest patients had higher mortality rates. Differences in treatrnent-limitation decisions between the lwo patient groups cannot be ruled out. We followed up the patients for 1 year. Although improvements are unlikely to occur beyond this period, some degree of conformation bias cannot be ruled out. In both cardiac arrest and TBI, neurologie injury and recovery is a dynamic process. Therefore, our findings are only valid within the studied lime (ie, the early subacute phase). In TBI, the spatial distribution varies across patients as a resullof variations in the direction of the impact on the head. Thalhighly significant results were found in our study despite this inevitable source of heterogenity supports the general applicability of our findings.

Our results should be tested in ruture research evaluating the robustness and validity of λ_1 and λ_1, preferably comparing the DT imaging results with postrnortem pathologie findings.

Although the neurologie presentation is similar in patients with persistent consciousness impairrnents after TBI and cardiac arrest, DT imaging findings suggest substantial differences in white malter injury between these lwo causes. Our findings indicate differences at bath the topographie and the cellular levels. The results in cardiac arrest patients are consistent with a primary axonal injury responsible for secondary myelin damage. In TBI in contrast, the chiefly mechanical primary mechanism results in myelin damage, which is followed by secondary ischemic injury. The consistency of ourfindings wilh current pathophysiologicconcepts supports the validity of DT imaglng for In vivo testing ofpathophyslologic hypotheses in humans. DT Imaging is a promising in vivo tool for separating myelin !rom axonal damage, a step that may prove important in the early prediction and understanding of patient outcomes.

Advances in **Knowledge**

- In cardiac arrest, the predominant finding al diffusion-tensor (DT) imaging is a marked decrease in axial diffusivity (λ_1) (-8.9% in central regions, -9.1% in cerebral hemispheres), whereas in traumatic brain injury (TBI), the predominant finding is a marked increase in radial diffusivity (λ_1) (37 .5% in central regions, 24.9% in cerebral hemispheres).

• The central brain structures show lower A1 and higher AL values in TBI!han in cardiac arrest (cardiac arrestvs TBI, *P*< .01 for A1 in the lower brainstem region and for AL in the cerebral peduncles region and corpus callosum region); in the cerebral hemispheres regions, A1 and AL are highly abnormal in both cardiac arrestand TBI, with the lowest A1 values occurring in cardiac arrest (cardiac arrestvs TBI, -9.1% vs - 0.1%; *P*< .01) and the highestAL values in TBI (TBI vs cardiac arrest, 24.9% vs 9.7%; *P*< .01).

• The known predominance of left-sided damage in TBI patients with poor clinical outcomes is attributable to left-sided predomlnance of AL abnormalltles and, to a lesser extent, A1 abnormalltles *(P* > .05 for slde-to-slde correlatlons In ftve of six ROIs for AL and In three of six ROIs for A1); this findlng suggests greater asymmetry of edema and/ormyelin damage !han of axonal damage in TBI.

Implications for Patient Care

• Our findings help physicians understand the mechanisms underlying chronic consciousness impairments after TBI and cardlac arrest.

• Our findings encourage physicians who interpret DT imaging studies to take into account not only scalar variables such as fractional anisotropy and apparent diffusion coefficient but also vector variables such as A1 and AL.

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