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An evaluation of the emerging techniques in sports-related concussion.

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Abstract

Sports-related concussion (SRC) is now in public awareness more than ever before. Investigations into underlying pathophysiology and methods of assessment have correspondingly increased at an exponential rate. In this review, we aim to highlight some of the evidence supporting emerging techniques in the fields of neurophysiology, neuroimaging, vestibular, oculomotor, autonomics, head sensor and accelerometer technology in the setting of the current standard: clinical diagnosis and management. In summary, the evidence we reviewed suggests that 1) head impact sensors and accelerometers may detect possible concussions that would not otherwise receive evaluation; 2) clinical diagnosis may be aided by sideline vestibular, oculomotor and portable EEG techniques; 3) clinical decisions on return-to-play eligibility are currently not sensitive at capturing the neurometabolic, cerebrovascular, neurophysiologic and microstructural changes that biomarkers have consistently detected days and weeks after clinical clearance. Such biomarkers include heart rate variability, quantitative electroencephalography, as well as functional, metabolic, and microstructural neuroimaging. The current challenge is overcoming the lack of consistency and replicability of any one particular technique to reach consensus.

Keywords

Concussion; Sports injuries; qEEG; neurophysiology; neuroimaging; techniques

Introduction

While there is no consensus clinical criteria for mild traumatic brain injury (mTBI), it has been defined by the American Congress of Rehabilitation Medicine as a traumatically induced physiological disruption of brain function characterized by at least one of the following: a period of loss of consciousness, a loss of memory for events immediately

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before or after the injury, an alteration of mental state at the time of the injury, or focal neurologic deficits (1). The traumatic brain injury would become moderate-severe if the loss of consciousness was greater than 30 minutes, the Glasgow Coma Scale was lower than 13 after 30 minutes, or if posttraumatic amnesia was greater than 24 hours. Other proposed criteria, such as from the Department of Defense, further require the diagnosis of mTBI to be absent of CT or MRI brain imaging abnormalities, and some new devices are being used to specifically assess for the presence of a bleed indicating a more severe injury (2, 3). The term concussion is often used interchangeably with mTBI but this is not based on precise criteria. Sport related concussion (SRC) can be viewed as a subtype of mTBI and has been defined as a traumatic brain injury induced by biomechanical forces which results in immediate and transient symptoms (4). Although pathological changes may occur, it is thought to primarily reflect a functional disturbance and is characterized by a variety of symptoms including headache, cognitive impairment, behavioral change, impaired balance, and sleep disturbance. The 5th international conference on concussion in sport has recently published a consensus statement to guide clinical care for SRC (4).

The first step in appropriately treating SRC is accurate recognition and diagnosis. This is accomplished through rapid sideline screening evaluations followed by a more thorough off-field assessment which includes cognitive, balance, and symptom evaluations. A standardized tool for this evaluation is the sport concussion assessment tool – 5th edition (SCAT5). If a concussion is suspected, an athlete should be removed from play and evaluated by a medical provider trained in the treatment of concussion. It is recommended that athletes rest for the first 24 to 48 hours until symptom free, and then enter a graduated return-to-play protocol, gradually increasing their level of activity until they can perform all the aspects of their sport without recurrent symptoms. Conventional neuroimaging is typically normal and often not required in SRC.

Despite our increase in the understanding of SRC, it remains a clinical diagnosis. Observers may miss a hit on the field and athletes may minimize symptoms leading to under-diagnosis and premature return to play. While previous editions of the SCAT5 were accurate in differentiating between athletes with and without a concussion during the first 24 hours, their utility decreased significantly 3–5 days after the injury (5). There also may be a difference between symptomatic and physiologic recovery. For example, while the majority of athletes are symptom free by 10–14 days, reliable studies of cerebral blood flow and magnetic resonance spectroscopy have indicated a physiologic disturbance between 15–30 days (6). Finally, approximately 15% of athletes have symptoms for at least 30 days, and we do not understand why this occurs or how best to manage these patients (7). These factors illustrate the need for improved technologies or biomarkers to aid in diagnosis and management of SRC.

In this review, we attempt to highlight the evidence behind some of the emerging techniques under investigation for diagnosis and management of SRC. There is increasing and consistent evidence across various subfields of concussion study demonstrating that microstructural, metabolic and functional brain changes persist beyond what can be detected with clinical and neuropsychological testing alone. This evidence suggests that athletes may be returning to play while the brain is still sensitized to superimposed injury from an additional concussion. Here, we discuss some of the studies which may improve sports concussion management through more sensitive detection and biomarker-guided recovery. Of note, while the focus of this review is on SRC, much of the research has been completed on mTBI from a variety of causes and we have included pertinent studies here.

Neurophysiology

Quantitative EEG (qEEG)—EEG was the first biomarker for traumatic brain injury, dating back to 1940 (8). Now qEEG allows for computer-based detection and quantification of patterns. EEG is inexpensive, non-invasive and accessible, even more-so now with FDA-approval of a portable handheld device in 2016 for assessment of TBI (9). Yet, surprisingly few studies have been conducted with EEG in sports concussion. In fact, a systematic review of resting state EEG (rsEEG) in sports concussion found only 16 studies through June 2017 (9), and 7 pediatric studies through December 2017 (8).

Power-based analysis: The most common analytic technique of qEEG, power-based analysis measures the magnitude of each frequency band (delta: 0–3 Hz; theta: 4–7 Hz; alpha: 8–13 Hz; beta: 14–30 Hz). These bands are associated with different arousal states, and alterations may be expected following SRC. Among 8 studies reporting specific frequency band data; 3 of 3 studies reported reduced alpha power and 4 of 4 reported increased delta power (9). Beta (3 of 5) and theta (3 of 4) power analyses had mixed results (9). Two pediatric studies add to these mixed results, reporting increased beta and reduced theta and delta (8). None of these studies acquired EEG prior to concussion to assess within-subject differences, which, along with varying methodology, may account for inconsistencies.

Coherence: Coherence detects network connectivity patterns through measuring the associative strength between activity (phase or amplitude) at two electrodes. As one may have axonal injury in concussion, it is hypothesized that there may be decreased coherence. Unfortunately, opposing results were reported from three available studies (9).

Novel analytic methods: Several non-standard analytic algorithms have been developed in an attempt to identify rsEEG characteristics that may be missed by conventional assessment. A prospective study used a support vector machine learning algorithm 30 days after injury and reported changes in temporal and occipital areas across theta, alpha and beta frequency bands with 96.7% sensitivity and 77.1% accuracy (10). The same group used a wavelet information quality (WIQ) algorithm in a prospective study in an attempt to monitor recovery. They found that although neuropsychological tests had normalized by day 7, even in athletes with two concussions, WIQ measures remained decreased after athletes were cleared to return to play (11). Interestingly, there was a differential rate of recovery among single vs. second concussion athletes (11). The same group reported consistent findings with a conceptually unique algorithm measuring the shifting of the dominant frequency over time, uniquely assessing peak frequency rather than amplitude (12). Another group has used composite scores combining metrics from 5 frontal leads and found impaired scores in athletes persisting well beyond 7 days, when all athletes had been cleared by neuropsychological testing (13, 14). Differences have been reported out to 6 months in

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athletes with normal neuropsychological batteries using event-related potentials (ERPs), which are an averaged signal in response to a stimulus (i.e. visual in this case) (15).

In summary, while the cost and feasibility of EEG is ideal, there is a lack of consistency among replicated analytic approaches, and novel algorithms require replication. Moreover, EEG depends on well-trained personnel to ensure quality data acquisition, and hands-on review to ensure artifacts are identified and removed. The most consistent finding from a recent systematic review is alterations in theta oscillations, including power and coherence (9, 10). This is interesting because theta oscillations have been reported outside the setting of concussion for roles in attention, memory, and wakefulness, but are also associated with suicidality and anxiety, and are reduced during periods of poor athletic performance (9). EEG has emerging clinical value as an aid in guiding return to play: multiple studies mentioned above, as well as a portable EEG device (16), describe EEG abnormalities persisting well beyond clinically-based return-to-play decisions in the setting of a still-recovering brain.

Magnetoencephalography (MEG)

MEG is approved for pre-surgical brain mapping, and works through detection of magnetic field changes produced by current flow through neurons. It has not been studied in sports-related concussion, but MEG insights from non-sports related mTBI have revealed abnormal functional connectivity and complexity signals. Analyzed from an algorithm designed to estimate the number of different MEG patterns in a sequence, MEG studies have revealed decreased complexity in multiple brain regions of veterans with mTBI (17). Functional connectivity was also abnormal across frontal, temporal and subcortical brain regions of 26 blast mTBI service members with persistent symptoms, compared to 22 active-duty controls (18). Encouragingly, MEG analysis revealed improved functional connectivity over longitudinal measures out to 42 months in a small cohort of TBI victims (19). MEG findings have demonstrated good specificity, with one study finding 85–87% corroboration with concussion symptoms (8); and by correlating with cognitive symptoms, but not with somatic or psychiatric symptoms (20).

Transcranial Magnetic Stimulation (TMS)

Repetitive TMS is FDA-approved for major depressive disorder, obsessive-compulsive disorder, smoking cessation, while single-pulse TMS is FDA-approved for migraine headaches. Single-pulse and paired-pulse TMS has been used in combination with EEG as a non-invasive probe of functional brain integrity (21). It is also used with electromyography (EMG) by assessing motor-evoked potentials (MEPs) in concussion (22–24). TMS delivers a magnetic pulse which induces current in neuronal fields by Faraday's law. The most consistent findings have been abnormalities in intracortical inhibition, with other findings being less consistent (21–24). In short, the role of TMS with EEG or EMG remains unclear.

Imaging

Structural

Computed Tomography (CT): CT does not have a role in the diagnosis of SRC, as abnormal findings would, by definition, rule out mild traumatic brain injury (25). It is instead appropriate to rule out more severe TBI in the setting of loss of consciousness, a Glasgow coma scale (GCS) <15, focal neurologic deficits, prolonged amnesia or signs of fracture or deterioration (26, 27).

Magnetic Resonance Imaging (MRI): MRI, as with CT, is not recommended for concussion diagnosis despite its common use for this purpose. For example, while only 8 out of 151 youth had abnormal findings in one study, they reported it was still used as a determinant of return-to-play (28). Its use for diagnostics is discouraged by the American Academy of Neurology and American Medical Society of Sports Medicine due to low yield (26, 27). However, multiple studies suggest utility in long-term prognostication. A recent SRC imaging review summarized multiple studies reporting detectible atrophy in the cortex and subcortical structures (29). For example, cortical atrophy has been observed in pediatric patients with mTBI at 4 months (30) and college football players with a history of concussion had smaller hippocampal volumes (31).

Diffusion MRI: Conventional MRI sequences are not sensitive to the axonal injuries which may occur in mTBI. Microstructural axonal changes can be detected by diffusion-weighted imaging (DWI), which measures white matter tract integrity through analyzing the direction of water diffusion. Diffusion tensor imaging (DTI), in turn, uses the raw data from DWI to create tractography, approximating white matter tracts. A comprehensive review by Shenton and colleagues reported 43 DTI studies of mTBI which all showed DTI abnormalities in the absence of macrostructural changes detectable on MRI (32). However, inconsistencies in the specifics of these changes have been the source of some confusion. There is a mix of increased and decreased fractional anisotropy (FA), a measure of degree of unidirectional water movement; and mean diffusivity (MD), a measure of the degree of multidirectional water diffusion. Hypotheses on the reasons for these discrepancies remain under investigation. DTI studies have shown a correlation with severity of injury and clinical outcomes (including reaction times) up to 1 year after injury (29). A more recent review reports 3 null studies out of 19 in pediatric concussion, but suggests more advanced analysis paradigms such as graph theory and multiple b-values may help clarify some of the remaining uncertainty (8).

Metabolic

Positron Emission Tomography (PET)—The utility of PET for SRC is limited by cost, accessibility and radiation exposure. To date, there have been no studies of PET in SRC. It is worth noting, however, that studies of mTBI have shown the potential for long-lasting metabolic sensitivity in symptomatic patients. In one case series, medial temporal hypometabolism was observed for up to seven years after mTBI (20, 33), and others observed 20/20 patients with clinical symptoms showing PET abnormalities 43 months post-injury (33, 34). Study design of PET imaging in mTBI has been variable, and additional controlled research is needed.

Magnetic Resonance Spectroscopy (MRS)—SRC is associated with numerous metabolic disturbances. MRS is able to detect such changes through altering the magnetic signals of individual chemicals. It is approved to evaluate brain tissue non-invasively for indications such as distinguishing tumor recurrence from radiation-induced necrosis, and determining tumor gradation. A systematic review of MRS in SRC found MRS abnormalities in 9 out of 11 studies. Importantly, there is evidence to suggest that metabolic changes outlast clinical symptoms, which is relevant for return-to-play considerations and superimposed concussions (35). For example, athletes who were clinically normal 3 days after concussion showed reduced n-acetylaspartate (NAA) through day 15, normalizing by day 30. Repeat concussions in these athletes extended MRS recovery time to 45 days (36). Alteration in the NAA peak (a marker for viable neurons) relative to the creatine peak is the most commonly observed abnormality. However, results are not all consistent, and include decreased choline, increased gamma-aminobutyric acid (GABA), and null findings (8).

Neurovascular coupling

Functional Magnetic Resonance Imaging (fMRI)—Notwithstanding the microstructural and metabolic changes discussed above, concussion is commonly considered a functional, rather than structural, pathology. fMRI is therefore an attractive non-invasive biomarker candidate which measures neuronal activity levels indirectly through differences in regional blood oxygen levels. It is used clinically to identify eloquent cortex for presurgical planning, and is widely used in research studies to understand brain function with good spatial resolution. Early studies reported bidirectional correlation between clinical scores and fMRI signals which resolved with clinical improvement and remained increased with poor recovery (34). Moving towards biomarker sensitivity exceeding clinical sensitivity, Dettwiler and colleagues found increased signal beyond neuropsychological test abnormalities in the dorsolateral prefrontal cortex at 2 weeks and 2 months (37). Regarding prognostication, another group found that athletes with increased fMRI signal in Brodmann's area 6 one week after concussion took twice as long to recover (38).

Resting state MRI (rsMRI) assesses the connections between brain regions. Rather than relying on a task to elicit changes in regional blood oxygen levels, blood oxygen level dependent (BOLD) signal changes are temporally associated with other areas of the brain during a relaxed or "default" state, including the default mode network (DMN). A longitudinal mTBI study reported increased anterior to posterior DMN connectivity at 1 month being predictive of increased symptoms at 3 months (39). Although not all studies agree on the direction of the signal abnormalities, there is a trend towards initial hyper-connectedness followed by hypo-connectedness, and finally normalization. Interestingly, abnormalities have been reported up to 5 years after injury (40).

Near-infrared Spectroscopy (NIRS)—NIRS measures cerebral blood volume and oxygenation through hemoglobin, and is FDA-approved for cerebral oximetry in patients at risk for regional ischemia. It has been used to follow hemodynamics in concussed patients

(20), and to identify the presence of hematoma in pediatric mTBI (8). Thus, although its cost and portability are attractive, its usefulness in SRC remains unknown.

Hemodynamics

Single Photon Emission Computerized Tomography (SPECT)—Compared to PET, SPECT is more affordable, more available, and has more evidence in concussion. SPECT measures cerebral blood flow with a gamma camera by tracking an injected radioisotope. There are dozens of FDA-approved indications for SPECT, each connected with a unique radiopharmaceutical allowing for identification of specific markers. SPECT is highly sensitive at predicting neuropsychological deficits. In non-SRC specific mTBI patients, SPECT scans and baseline neuropsychological testing were taken within 2 weeks of injury. Neuropsychological testing was then performed at 6 and 12 months. Authors found that a negative SPECT scan near time of injury predicted normal neuropsychological testing with 100% negative predictive value. A positive SPECT scan predicted abnormal testing with 52% and 83% positive predictive value, respectively (41). Collectively, 94% of SPECT scans reviewed from 26 studies of non-SRC specific mild to moderate TBI showed hypometabolism in frontal lobes, followed by temporal (76%), parietal (71%), occipital (53%) and cerebellum (23%) (41).

Ultrasound—Cerebral vasoreactivity alterations following pediatric mTBI occur in the acute setting. Evidence with this technique is limited, but high specificity (97%) and sensitivity (90%) has been reported from 7.2% of a sample of 256 ER pediatric patients (8). A systematic review in 2015 reported that all three available studies found a reduction in vasoreactivity in the acute setting, normalizing 4–5 days after injury (42). Based on the strong but limited data, this portable and affordable technique holds promise for diagnosis in the acute setting, though user experience and inter-observer variability may be a limiting factor.

Arterial Spin Labeling (ASL) & Dynamic Susceptibility Contrast (DCS)—ASL is a non-contrast alternative to DCS MRI which measures regional cerebral blood flow (CBF). Maugans and colleagues reported changes in contrasted blood flow immediately after SRC which gradually normalized in the majority of patients over 30 days (43). In a recent ASL study of 15 concussed athletes, increased CBF was observed in the left insula lasting two weeks, and in the left dorsal anterior cingulate cortex lasting 6 weeks (44).Unfortunately, consistency is lacking among the findings of the 12 reported ASL studies (44).

Autonomic Dysfunction—One of the vulnerable regions to mechanical stress experienced during concussion is the brainstem; a location integral to the control of the autonomic nervous system. It thus follows that concussion causes autonomic nervous system dysfunction. Autonomic dysfunction is now commonly measured as a sequela of concussion, and has been correlated to clinical symptomatology; this has been seen with changes in parameters of heart rate variability, pupillary dynamics, and cerebral blood flow, among other measures.

Heart rate variability (HRV): HRV is the most commonly studied measure of autonomic dysfunction following concussion. 24-hour HR variability recording is effective in measuring the impact of concussion on autonomic function (45). A number of case control studies have taken baseline measurements of a group of athletes, and then again after concussion injuries. HRV was observed to decrease down to 26% (46), and measurable changes in HRV can persist up to three months (47). Changes in HRV also correlate with post-concussion symptoms. For example, one interesting cross-sectional study by Paniccia and colleagues examined non-concussed study subjects' 24-hour HRV and found a significant positive correlation with degree of symptoms reported on a post-concussion inventory (48). Another recent case-control study found that decreased HRV was associated with symptomatology, in this case with increased anxiety (49). Some authors suggest that following changes in HRV over time may be useful in guiding return-to-play decisions (47).

Vascular Tone: Changes in autonomic control of vascular tone occur immediately following concussion, and persist beyond the immediate post-concussion period. Concussion causes reduced baroreceptor sensitivity for at least a week following the injury (50). Related to this, concussed individuals experience significant reductions in the pressure-buffering capacity of the cerebral blood vessels for at least 2 weeks following injury as measured by transcranial doppler (51). No protocols currently exist for using this data in the diagnosis or management of SRC.

Other Measures: While most recent papers on autonomic dysfunction and concussion have examined heart rate or vascular tone, a few other measures deserve mention. Several studies have shown that concussion causes slowed pupillary responsiveness to light (52). Another study explored the sensitivity of the respiratory drive to carbon dioxide and found that subjects with recent concussion had significantly elevated end-tidal CO_2 during rest and during cognitive assessment with both slow and fast walking compared to control group (53).

In summary, the usefulness of objective measures of autonomic dysfunction in the diagnosis or treatment of concussion is uncertain. As above, autonomic dysfunction has been correlated with degree of post-concussion symptomatology. In terms of assisting recovery, several studies have examined using heart rate parameters to develop graded exercise programs (54). This research appears promising, though more data needs to be gathered before official recommendations could be made.

Head Impact Sensors—One technology being studied to increase the sensitivity of SRC detection and to determine the factors that lead to it are head impact sensors and accelerometers, which are able to measure the linear and angular acceleration of a head impact during play. In theory, if a certain threshold is reached, the sensors would notify a monitor to take an athlete out of the game for an evaluation. Error rates, as high as 50% in some studies, currently limit their clinical utility (4, 55). Further, a change in acceleration is not a direct measurement of brain impact, and thresholds needed for concussion have not yet been determined. Thus, head impact sensors are not currently recommended for clinical use (4, 55).

Vestibular & Oculomotor—The vestibular system can be affected immediately in SRC and consequent abnormalities with balance, gait, and eye movement can be among the most debilitating sequalae (56). A vestibular clinic classified 58 patients into 3 categories of dizziness: positional vertigo, spatial disorientation, and migrainous. They followed time to symptom progression and return to work and found that the spatial disorientation group had markedly slower recovery time (39 and 16 weeks, respectively) compared to the migraine group (8 and 4 weeks) and the vertiginous group (less than 1 week for both) (57). These findings highlight the variety and disabling potential of vestibular injury in TBI. As such, several aspects are tested in SRC and TBI.

First, balance is commonly assessed in the acute setting by using a modified version of the balance error scoring system (mBESS) which is part of the SCAT5 and its previous versions. The mBESS assesses balance in an organized manner by asking an athlete to hold certain postural positions (such as standing on one foot) for 20 seconds. While this tool is felt to be the most reliable and practical tool for assessing SRC acutely, there have been some questions about interrater reliability and its utility beyond 5 days (5). To address these limitations, pressure sensing technology is being studied. Devices with a pressure sensitive mat or a balance board have been shown to have equivalent or better validity and test-retest reliability compared to human scorers on normal subjects (58, 59). Second, posture can be tracked with wearable sensors. For example, a lumbar sensor measuring postural sway was compared to mBESS in symptomatic patients within four days of concussion. The sensor was able to detect group differences, whereas the mBESS did not (60).

Eye movement abnormalities are tested with Vestibular/Ocular Motor Screening (VOMS) which incorporates smooth pursuit, vertical and horizontal saccades, near point of convergence, vestibulo-ocular reflex (VOR), and visual motion sensitivity. VOMS has been shown to have good internal consistency, sensitivity and specificity, and correlates well with post-concussion symptom scales (PCSS) (61). VOMS detected greater deficits in females than males 21 days out from SRC which matched PCSS scores, even while balance and cognitive testing detected no differences (62). A marketed version of VOMS has athletes quickly read a series of irregularly spaced numbers. Performance slows after concussion. A meta-analysis of this method reported a sensitivity of 86%, and a specificity of 90%, for detecting SRC (63). However, this method requires within-subject comparisons, so baseline testing is required. Similarly, eye-tracking technology, which monitors pupil position while following moving visual stimuli, reports good sensitivity and specificity with an area of 0.878 under a receiver operating characteristic curve (64). The promise of this approach is supported by findings with video head impulse testing. Here, gaze is fixed on a visual spot and video recorded while the head is shifted. This test performed as well as the gold standard test (scleral search coil technique), but is much quicker and easier to perform (65). Another test of the VOR, the dynamic visual acuity test (DVAT) is a rapid computerized screening tool that reliably quantified TBI recovery over 1 month (66). In a study of 42 pediatric SRC patients with protracted dizziness, DVAT was the most sensitive among a comprehensive vestibular battery (67). While these new technologies are promising, additional research is required to assess their validity and practicality before they are recommended for routine clinical use.

Computerized testing—Athletes with SRC commonly experience cognitive symptoms such as slowed reaction time, attentional difficulties, and feeling “like they are in a fog”. Neuropsychological testing can characterize an athlete’s deficits and inform the decision to return to play. It can also be useful in determining the underlying etiology of prolonged cognitive symptoms, whether they are from an underlying neurologic injury or another cause. Unfortunately, neuropsychologists are not available to assess every athlete with an SRC. To fill this gap, computerized neuropsychological assessments have been developed, and many have been marketed. A recent comprehensive review assessed their validity compared to formal neuropsychological testing; and unfortunately, results were mixed, and test-retest reliability was not consistent (69). With further study and development, computerized testing will likely have a role in the diagnosis and treatment of SRC.

Conclusion

As public interest has grown, the research into SRC has rapidly expanded. However, there is still no gold standard for the diagnosis of concussion and questions remain regarding diagnostic accuracy, the persistence of physiologic dysfunction beyond clinical symptoms, appropriate time to return to play, and long-term sequelae. In this review, we attempted to highlight the evidence behind some of the emerging techniques under investigation for diagnosis and management of SRC. While most require further study, there have been promising results. Going forward, sensitivity of the on-field diagnosis of concussion may be enhanced by head impact sensors, oculomotor tracking, and portable EEG. MRS, qEEG, and autonomic testing may surpass symptom report in making return to play decisions. Functional imaging and DTI may be used to determine risk for long term cognitive dysfunction. It is beyond the scope of this article to examine every new technique under evaluation. However, as further research is completed and replicated, we expect some of the emerging techniques described here to become standard of care.

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