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Relationship between Clinical Findings and Quantitative Electroencephalographic Variables in Comatose Patients

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By quantitatively analyzing the electroencephalograms (EEGs) of comatose patients, we defined and determined quantitative EEG variables (QEVs) as brain function indicators. The objective of the present study was to investigate the relationship of QEVs to clinical findings and EEG findings and ascertain the usefulness of QEVs. Subjects were 70 comatose patients and 15 patients with normal EEG (control group). EEGs were recorded using eight electrodes and subjected to fast Fourier transformation (FFT) (analysis time : 20 seconds) three consecutive times. Based on the results of three FFT analyses, QEVs were defined and measured, and their intercorrelations and relationships to the cause of consciousness disturbance, consciousness level, prognosis, and EEG findings were evaluated. The results confirmed a significant inverse relationship between two QEVs. Moreover, multiple comparison analysis showed significant differences in QEVs between the control and comatose groups and among EEG patterns. Discriminant analysis of QEVs showed $\geq$ 70% concordance rates for EEG patterns, symmetry, and pain response. QEVs appear to be useful for assessing the brain function of comatose patients.

Key words

EEG analysis, Quantitative EEG variables, Coma, Absolute power, Relative power

Introduction

Electroencephalography (EEG) in consciousness disturbance yields various information, such as the severity of central nerve disorders, efficacy of therapeutic drugs, and prognosis[1)-3)]. Because EEG is noninvasive and convenient, it is extremely useful in monitoring brain function[4)]. There have been many reports on EEG findings in comatose patients, and the relationship between EEG and clinical findings has been examined from different perspectives[5)-9)].

In recent years, with the introduction of digital EEG, the storage and secondary processing of EEG data have markedly improved. With most recent digital EEG equipment, EEG spectral analysis software makes it easy to quantitatively analyze EEG data in routine clinical settings[10)]. While the conditions for quantitative EEG analysis have improved, techniques for visualizing EEG data such as frequency mapping and potential mapping remain the most common methods in clinical

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use[11], and brain function has not been assessed using more objective quantitative data.

In the present study, we quantitatively analyzed EEGs of comatose patients obtained by digital EEG using an online system, and we defined and determined quantitative EEG variables (QEVs) as new indicators of brain function. QEVs can be measured by simple computations, and they can be used to quickly assess consciousness disturbance. Here, the interrelationships among QEVs and the relationships of QEVs to visual EEG findings and clinical findings were examined to ascertain the usefulness of QEVs as indicators of brain function in comatose patients.

Subjects and Methods

Subjects

Subjects were 70 comatose patients who were admitted to the ICU of Nagoya University Hospital and underwent EEG (36 men and 34 women) and 15 patients without consciousness disturbance who underwent EEG at the same hospital (8 men and 7 women) (control group). Average age was 55.3 years (standard deviation (SD) : 21.8 years, range : 2-89 years) for the comatose group and 68.7 years (SD : 10.0 years, range : 51-85 years) for the control group. The following clinical findings were retrospectively analyzed : etiologic type of consciousness disturbance (A : anoxic consciousness disturbance, O : organic consciousness disturbance, M : metabolic consciousness disturbance, and T : toxic consciousness disturbance), consciousness level at the time of EEG (0 : Japan coma scale (JCS) score of 0, I : JCS scores of 1-3, II : JCS scores of 10-30, and III : JCS score of 100-300) and prognosis (died within one week of EEG, died within one month of EEG, and alive at the time of the study).

EEG recording

Measurement of EEG was performed using digital EEG equipment (Bio-Logic System), and EEG data were recorded with the 10/20 method using eight electrodes (Fp 1/Fp 2, C 3/C 4, 01/02, and T 3/T 4) by average reference derivation. Digital recording of EEG was carried out under the following conditions : resolution 12 bits, sampling rate 256 Hz, low-pass filtering 0.5 Hz, and high-pass filtering 100 Hz. EEG was recorded for 10 minutes in comatose patients with the eyes closed in a resting state and in control patients with the eyes closed in an awake but resting state. For each subject, all records were visually reviewed prior to analysis, a period of at least 60 seconds where there was no noise was extracted, and FFT analysis was performed to calculate QEVs. EEG patterns were classified visually according to Gehhard[12] as follows : normal (Nor), within normal limits (WNL), slow waves (SW), epileptic discharges (ED), low voltage (LV), burst suppression pattern (BS), and electrocerebral inactivity (ECI). Pattern symmetry, pain response, and discontinuous patterns were evaluated.

EEG analysis

Digital EEG data were analyzed quantitatively using Brain Atlas (Bio-Logic System). Fast Fourier transform (FFT) analysis was performed three times under the following conditions : frequency resolution 0.5 Hz and analysis time 20 seconds (averaging ten 2-second periods). In each FFT analysis, the absolute power of the EEG wave at four frequency bands (δ band : 1.5-3.5 Hz, θ band : 4.0-7.5 Hz, α band : 8.0-13.0 Hz, and β band : 13.5-23.5 Hz) was calculated (δ, θ, α, and β band absolute power, or δ-AP, θ-AP, α-AP, and β-AP, respectively) for each electrode position.

QEV calculation and assessment

In each FFT analysis, total absolute power (TAP) was calculated as the sum of the absolute power values (AP) of 4 frequency bands

at all electrodes. Subsequently, the mean and coefficient of variation (CV) for three FFT analyses period were calculated (mean of TAP and CV of TAP, respectively). In addition, slow wave relative power (SWRP) was calculated by dividing the sum of δ-AP and θ-AP at all electrodes by TAP, and the mean and CV of SWRP were determined (mean of SWRP and CV of SWRP). Furthermore, in each FFT analysis, TAP symmetry and SWRP symmetry were calculated by dividing the value of left electrodes by that of right electrode (inverse numbers if less than one). Based on the average of three FFT analyses, maximum total absolute power ratio (max TAPR) and maximum slow wave relative power ratio (max SWRPR) were calculated. Additionally, because the mean of TAP ranged widely from 6.7 to 11913.7, log (mean of TAP) was used. The interrelationships among the above QEVs, i.e., log (mean of TAP), CV of TAP, mean of SWRP, CV of SWRP, max TAPR, and max SWRPR, and the relationships of QEVs to visual EEG findings and clinical findings were investigated. Discriminate analysis was conducted using QEVs as independent variables and EEG and clinical findings as dependent variables to ascertain whether or not EEG and clinical findings could be predicted based on QEVs. Table 1 summarizes the outline of EEG findings assessed by QEVs.

Statistical analysis

Statistical analysis was carried out using SPSS for Windows (version 11.0, SPSS, Chicago). Spearman's rank correlation coefficients were calculated and Kruskal-Wallis and Bonferroni's multiple comparison tests were employed. Stepwise discriminant analysis (F-value probability : 0.05 inclusion and 0.1 exclusion) was conducted. In all statistical analysis, values of $p<0.05$ were considered to indicate statistical significance ; all tests were two-tailed.

Results

Table 2 summarizes the clinical findings. In the comatose group, there were 15 cases each of WNL, LV and ECI, 11 of SW, 8 of ED, and 6 of BS. Asymmetry was seen in 18 cases, pain response in 18, and discontinuous EEG in 13. At the time of EEG, JCS scores were in single digits for 12 cases, double digits for 8, and triple digits for 50. The type of consciousness disturbance was A in 30 cases, O in 26, M in 9, and T in 5. As to prognosis, 30 patients were alive at the time of the study, 23 died within one week of EEG, and 17 died within one month of EEG. In the control group, none of the patients had a history of severe central nervous system disorders, all patients were conscious and exhibited no EEG abnormality at the time of EEG, and all were alive at the time

Table 1. Outline of EEG findings assessed by QEVs

QEVs	Assessment of EEG findings
Log(Mean of TAP)	EEG activity
CV of TAP	fluctuation of EEG activity
Mean of SWRP	percentage of slow wave
CV of SWRP	fluctuation of slow wave percentage
Max TAPR	Asymmetry of EEG activity
Max SWRPR	Asymmetry of Slow wave percentage

Table 2. Clinical outline

	Patient's group	Control's group
Number of subjects	70	15
Male : Female	34 : 36	8 : 7
Age (mean±SD)	55.3±21.8	68.1±10.0
EEG findings		
Pattern (cases)	WNL ; 15 SW ; 11 ED ; 8 LV ; 15 BS ; 6 ECI ; 15	N ; 15
Asymmetry (cases)	− ; 52 + ; 18	− ; 15
Responsibility (cases)	− ; 52 + ; 18	+ ; 15
discontinuous EEG pattern (cases)	− ; 57 + ; 13	− ; 15
Consciousness level with JCS (cases)	1−3 ; 12 10−30 ; 8 100−300 ; 50	0 ; 15
Etiologic type (cases)	anoxic ; 30 organic ; 26 metabolic ; 9 toxic ; 5	—
Prognosis (cases)	alive ; 30 died within 1 week ; 23 died within 1 month ; 17	alive ; 15

Abbreviations
N : Normal WNL : Within normal limits SW : Slow Waves ED : Epileptic discharges LV : Low Voltage
BS : Burst Suppression ECI : Electro Cerebral Inactivity

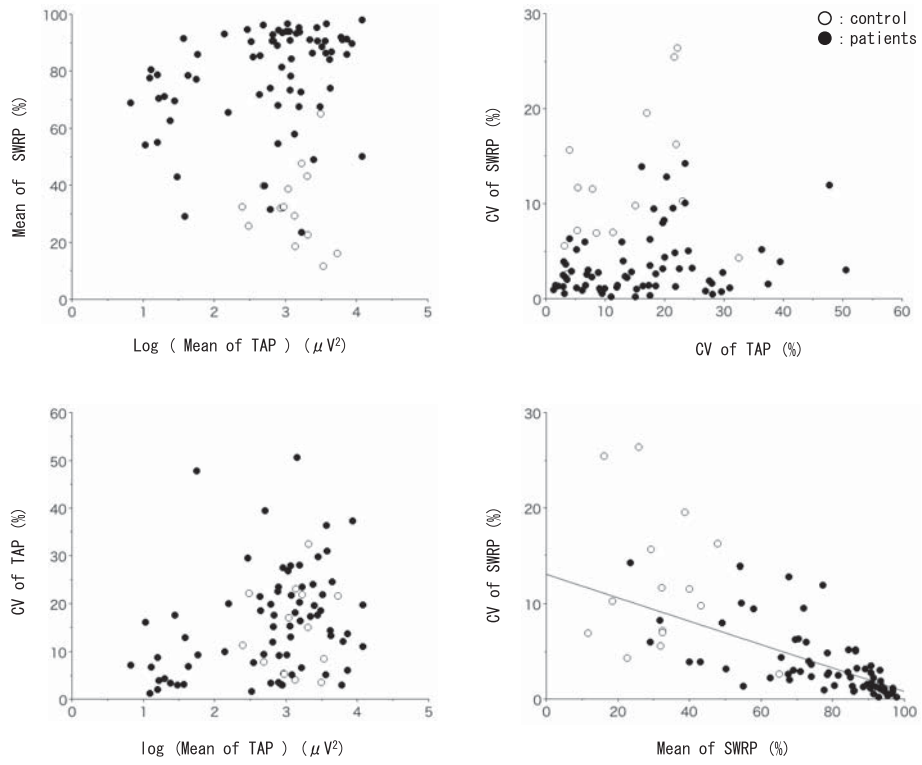

Figure 1. Interrelationships among EEG variables
The figures show interrelationships among EEG variables for the comatose patients (●) and control patients (○). For the comatose patients, a significant inverse correlation was seen between mean of SWRP and CV of SWRP.

of the study.

Interrelationships among log (mean of TAP), CV of TAP, mean of SWRP and CV of SWRP were assessed, and only for the comatose group, a significant inverse correlation was found between mean of SWRP and CV of SWRP (Spearman's ρ : −0.752, p<0.001) (Figure 1).

Table 3 lists significant differences in QEVs with respect to clinical findings. With all clinical findings, there were significant differences in at least one QEV, and significant differences were seen with mean of SWRP, CV of SWRP, and max SWRPR with respect to all clinical findings except for prognosis.

Multiple comparison analysis was conducted on QEVs and EEG patterns, and the results showed that with the exception of CV of TAP, significant differences existed in QEVs between the control group and the comatose group for each EEG pattern. Log (mean of TAP) for Nor was 3.09 μV^2, that for WNL and SW was slightly higher, and that for ED was the highest at 3.68 μV^2. Log (mean of TAP) for LV and SB was low, and that for ECI was the lowest at 1.32 μV^2. The mean

Table 3. Multiple comparison of EEG variables with respect to clinical findings

Clinical findings			Quantitative EEG Variables (QEV)					
category	comparison		log (Mean of TAP)	CV of TAP	Max TAPR	Mean of SWRP	CV of SWRP	Max SWRPR
Asymmetry	+	−		*	*	****	*	***
Response	+	−	*		*	****	****	
Dyscontineous	+	−				*	*	*
Consciousness level	0	I				**	*	*
	0	II				*	*	**
	0	III			*	**	**	*
	I	II						
	I	III						
	II	III						
Etiologic type	Contol	Toxic						
	Contol	Metabolic				**	**	*
	Contol	Organic				**	**	*
	Contol	Anoxic	*		**	**	*	
	Toxic	Metabolic						
	Toxic	Organic						
	Toxic	Anoxic						
	Metabilic	Organic						
	Metabilic	Anoxic	*					
	Organic	Anoxic	*					
Prognosis	Alive	died within 1 M	***		**			
	Alive	died within 1 week						
	died within 1 M	died within 1 week						

*P<0.05 **p<0.01 ***p<0.005 ****p<0.001

Significant differences existed in QEVs with respect to EEG and clinical findings. Regarding the QEVs, significant differences were often seen in slow-wave-related variables such as mean of SWRP, CV of SWRP, and max SWRPR. Moreover, among the EEG patterns, significant differences were seen in log (mean of TAP).

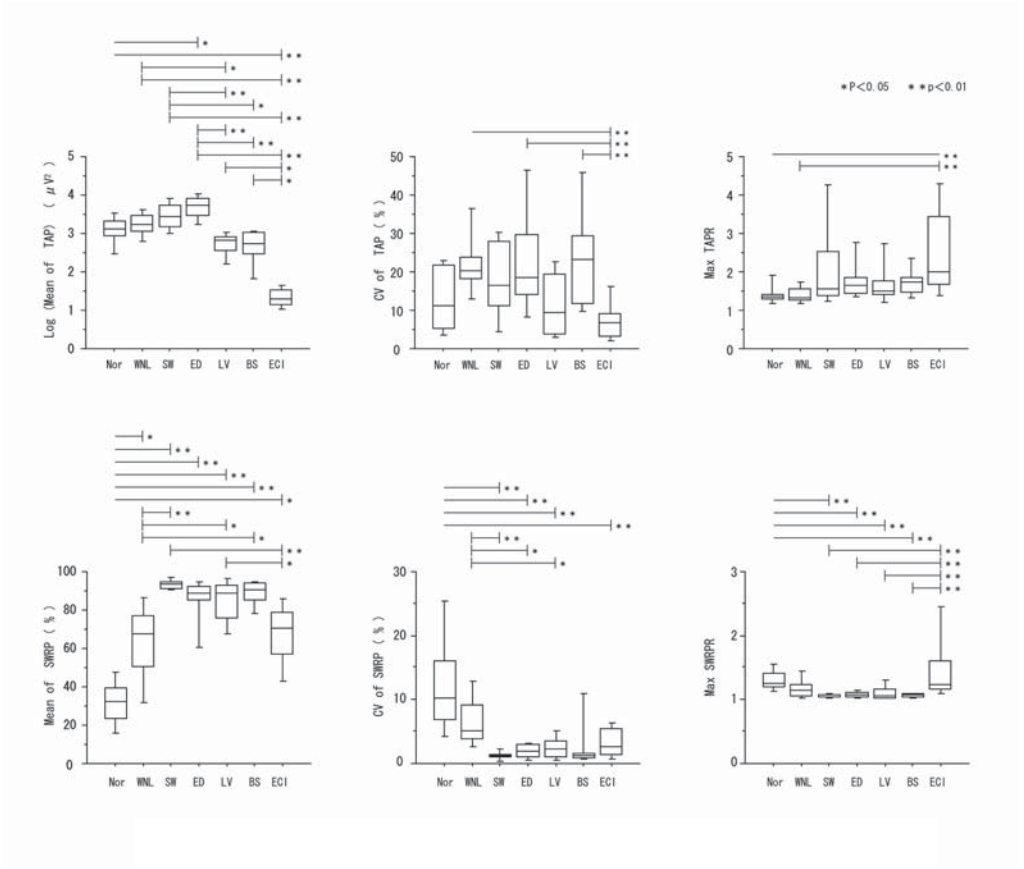

Figure 2. Box-plots of EEG variables with respect to EEG patterns
The figures show the relationship between EEG variables and EEG patterns. Significant differences were seen in all variables with some EEG patterns, but with log (mean of TAP) and mean of SWRP, there were significant differences between the control and comatose groups and among the EEG patterns.

of SWRP for Nor was the lowest at 32.5%, that for WNL and ECI was almost comparable (63.3 and 67.8%, respectively), and that for the other patterns was higher, ranging from 84.3 to 93.3%. There were less significant differences in CV of TAP among the EEG patterns, and significant differences were seen only between ECI and BS, ED, or WNL. CV of SWRP for Nor was the highest at 12.01, followed by that of WNL at 6.66, but that of the other patterns was low, ranging from 1.28 to 3.65. Significant differences existed in max SWRPR between Nor and SW, ED, LV, and BS (Figure 2).

In order to ascertain the possibility of estimating EEG and clinical findings based on QEVs, discriminant analysis was performed by using QEVs as dependent variables and EEG patterns and clinical findings as independent variables. The results indicated that it would be possible to predict EEG pattern, asymmetry, and pain response with $\geq$70% concordance rates. In terms of EEG patterns, the concordance rates for Nor and ECI were $\geq$85%, while that for SW was low at 45%. The concordance rate for positive asymmetry was 83.3%, and that for negative pain response was 82%. Concordance rates were low

for consciousness level I (25%), organic consciousness disturbance (15.4%), and acute-phase mortality (39.1%) (Table 4).

Discussion

In clinical settings, EEG data are interpreted visually based on frequency, amplitude, phase, form and distribution, but visual EEG analysis is qualitative, and responsiveness is classified based on the discretion of readers[13)14)]. When examining comatose patients, it is necessary to objectively and quickly interpret EEG data, and since long-term follow-up is sometimes required, attempts have been made to quantitatively analyze EEG data using computer programs[15)-19)]. Here, we quantitatively analyzed the EEG findings of comatose patients, and QEVs were defined and determined as new indicators of brain function. Their characteristics and correlations to clinical findings were examined.

As to the interrelationships among QEVs, for the comatose group, an inverse correlation existed between mean of SWRP and CV of SWRP. This indicates that more frequent appearance of slow waves in comatose patients, the lesser the variation. It has been well documented that as brain function diminishes, slow waves appear more frequently. According to Bricolo et al.[20)], prognosis was poor for comatose patients with no variations in EEG power spectrum. Furthermore, in one study on the compress spectrum array (CSA) of head trauma patients, spectral patterns with less variation in activity indicated high mortality rates, thus suggesting that CSA is a useful prognosticator[21)]. In other words, more frequent appearance of slow waves indicates low brain function, and, in comatose patients, little variation represents poor prognosis.

As to the relationship between QEVs and EEG patterns, significant differences were seen in all QEVs among some EEG patterns, and with log (mean of TAP), mean of SWRP, and CV of SWRP, significant differences were

Table 4. Discriminant analysis

Dependent variable (Stepwise method)	Predictor variable	Proportion of right answers (%)	
EEG pattern	log (Mean of TAP) Mean of SWRP CV of TAP Max TAPR	Total 71.8	Nor ; 86.7 WNL ; 60.0 SW ; 45.5 ED ; 62.5 LV ; 73.3 BS ; 50.0 ECI ; 100
Asymmetry	Mean of SWRP CV of TAP	75.3	− ; 73.1 + ; 83.3
Response	log (Mean of TAP) CV of SWRP	76.5	− ; 82.0 + ; 68.6
Dyscontinuous	Mean of SWRP	57.6	− ; 52.8 + ; 84.6
Level	log (Mean of TAP) Mean of SWRP	60.0	0 ; 93.3 Ⅰ ; 25.0 Ⅱ ; 75.0 Ⅲ ; 56.0
Type	log (Mean of TAP) Mean of SWRP Max SWRPR	50.6	Control ; 93.3 Toxic ; 40.0 Metabolic ; 55.6 Organic ; 15.4 Anoxic ; 60.0
Prognosis	log (Mean of TAP) Mean of SWRP	60.0	alive ; 71.1 dead ; 58.8 dead (acute) ; 39.1

Discriminant analysis of QEVs with respect to EEG and clinical findings showed that the concordance rates for EEG findings were relatively high at 72-77%, while those for clinical findings were lower at 50-60%.

seen between the control and comatose groups and among EEG patterns, thus suggesting that it may be possible to estimate EEG patterns based on QEVs. Slow waves are an indicator of low brain function, and, as shown in Figure 2, it appears valid to define abnormal EEG as $\geq$50% mean of SWRP and <5% CV of SWRP. Another indicator of low brain function is ECI. Although there were significant differences in QEVs with the other EEG patterns, the significance of FFT analysis of poor EEG activities is low for ECI because slight noise has a marked impact on the outcomes.

With regards to the relationship between QEVs and clinical findings, significant differences were seen in slow-wave-related variables such as mean of SWRP, CV of SWRP and max SWRPR with respect to almost all clinical findings, thus suggesting that the appearance of slow waves (the main change in EEG data) are reflected in clinical findings. When focusing on the cause of consciousness disturbance, there were differences in QEVs related to slow wave and TAP between anoxic consciousness disturbance and the other causes, thus agreeing with the results of a study documenting that total power was the best indicator for cerebral ischemia[22] and with a study focusing on the changes in slow wave bands as an indicator for cerebral ischemia[23]. Moulton et al.[24] investigated the relationship between Glasgow coma scale (GCS) and EEG power spectrum analysis in head trauma patients, and they reported a significant relationship between EEG amplitude and GCS and a marked relationship between EEG and the chronological changes in GCS. Moreover, Häkkinen et al.[25] examined 20 comatose patients and reported that prognoses could be predicted favorably based on CSA and GCS and that CSA was a technique independent of GCS for monitoring comatose patients. Furthermore, Matousek et al.[26] reported a correlation between slow waves and score on another coma scale, RLS 85 (reaction level scale 85). Regarding the relationship between QEVs and JCS levels, a significant difference existed in SWRP between the control group (JCS : 0) and comatose group (JCS : 1, 2 and 3), but no significant difference existed in QEVs among JCS levels 1, 2, and 3. This shows the difficulty in analyzing clinical findings based solely on EEG data. Oken et al.[27] also stated that various issues must be addressed before clinically applying qualitative EEG analysis.

Discriminate analysis of clinical findings showed that the concordance rates of QEVs varied. The concordance rates for two EEG patterns (Nor and ECI), positive asymmetry and negative pain response were above 80%, but those for consciousness level I, organic consciousness disturbance and acute-phase mortality (died within one week of EEG) were low at 25, 15.4 and 39.1%, respectively, and it was difficult to predict these factors based solely on QEVs. The reason for the low concordance rates was that diverse EEG patterns made it difficult to extract characteristic features. In addition, the concordance rate of QEV for survival was 71.1%, thus agreeing with Moulton et al. Hence, it is possible to estimate prognosis (survival) to a certain degree based on QEV.

In recent years, brain function monitoring units based on quantitative EEG analysis have been widely used in operating rooms and ICUs[28)-30)]. Moreover, in clinical settings, EEG frequency analysis has been added, and quantitative analysis of QEVs is beginning to be performed more often as a tool for interpreting EEG data. The QEVs in the present study can be conveniently calculated by EEG spectral analysis, and because QEVs can objectively evaluate EEG and clinical findings in comatose patients, they may be useful indicators for assessing EEGs in consciousness disturbance in clinical settings.

Conclusions

1) In comatose patients, EEG was quantitatively assessed by frequency analysis to determine QEVs, and the correlations of these QEVs to clinical findings were investigated.
2) Interrelationships among QEVs were investigated, and an inverse correlation was confirmed between mean SWRP and CV of SWRP.
3) Significant differences in QEVs were seen for all clinical findings, and the concordance rates, as ascertained by discriminant analysis of QEVs, for EEG patterns, asymmetry and pain response were $\geq$70%.
4) The results suggest the possibility of objectively assessing the EEG and clinical findings of comatose patients based on QEVs.

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