Anesthesiology
47:498–503, 1977

Atrioventricular Conduction Times and Atrioventricular Nodal Conductivity during Enflurane Anesthesia in Dogs

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Because alterations in conduction may be important as a cause of arrhythmias during anesthesia, the authors used His-bundle electrocardiography to evaluate the effects of enflurane on atrioventricular (AV) nodal, His–Purkinje, and ventricular conduction times in dogs. Evaluations were made in hearts beating spontaneously and during atrial pacing at rates between 120 and 200 beats/min. To test the effects of enflurane on the atrial effective refractory period, functional refractory period of the AV node, and AV nodal conductivity, atrial extrastimuli (test beats) were delivered at various cycle lengths (500 msec or less) after the last of a series of paced beats at 120 or 200 beats/min. AV nodal conductivity was evaluated by measurements of minimum conduction time, fatigue (the relation of minimum conduction time to change in heart rate), and interval-related conductivity (the prolongation of AV nodal conduction time beyond minimum conduction time related to prematurity of test response). Increasing concentrations of enflurane from 1.0 to 2.0 MAC prolonged AV nodal, but not His–Purkinje or ventricular, conduction times. AV nodal conduction time increased as heart rate was increased, and this rate-dependency was enhanced by enflurane. His–Purkinje and ventricular conduction times were not affected by rate or enflurane. The atrial effective refractory period, functional refractory period of the AV node, and AV nodal conductivity were depressed by enflurane. For the His–Purkinje and ventricular conduction system, the present results are in contrast to those previously reported for halothane. Conduction changes are necessary for ventricular arrhythmias caused by re-entry of excitation. These findings may in part explain the clinical impression that ventricular arrhythmias appear less likely to occur with enflurane than with halothane. (Key words: Heart, arrhythmias; Heart, atria; Heart, conduction; Heart, His bundle; Heart, electrocardiography; Anesthetics, volatile, enflurane.)

CARDIAC ARRHYTHMIAS have been attributed to anesthetic suppression of dominant pacemakers with enhancement of automaticity in latent pacemakers.[1,2] However, Cranefield[3] states that it is difficult to induce sufficient automaticity in ventricular Purkinje fibers and, in the case of halothane, both *in vitro*[2,4,5] and *in vivo*[6] studies show that ventricular automaticity is suppressed. Considerations such as these suggest that anesthetics may cause arrhythmias by their effects on atrioventricular (AV) conduction. Indeed, Sasyniuk and Dresel,[7] and Zink *et al.*[8] provide evidence that ventricular arrhythmias induced by epinephrine during cyclopropane[7] or halothane[8] anesthesia are caused by re-entry of excitation, a mechanism that requires altered conduction. While these authors believe the re-entry site to be within the left ventricular septum, it is conceivable that an AV nodal site combined with aberrant ventricular conduction may also be responsible.

We previously showed that halothane slows AV nodal, His–Purkinje, and ventricular conduction times in a dose-related manner.[9,10] More recently, we evaluated the effects of halothane on the conductivity and functional refractory period of the AV node.[11] Changes in conductivity of the AV node may be important in providing the necessary conditions for re-entry within this structure, or in affecting the conduction of potentially re-entrant impulses from above. The present study was undertaken to determine whether enflurane has different effects on AV conduction time and AV nodal conductivity than those previously reported for halothane. Such differences may explain in part the clinical observation that ventricular arrhythmias are less likely with enflurane than with halothane.[12]

Methods

Eighteen unpremedicated dogs of either sex (average weight 14.2 kg) were each anesthetized on a single occasion with a concentration of enflurane sufficient to produce an end-expired concentration (Beckman Infra-red Analyzer, Model LB-2) of 2.2, 3.3, or 4.4 per cent, equivalent to 1.0, 1.5 and 2.0 MAC (minimum alveolar anesthetic concentration), respectively.[13] Enflurane and oxygen were delivered to a circle absorber system from an Etec® vaporizer. Decamethonium, 3–5 mg, iv, was used to facilitate tracheal intubation and as necessary to prevent spontaneous movement during anesthesia. Respiration was controlled (Ohio, anesthesia ventilator) to maintain end-tidal P_{CO_2} (Beckman-red Analyzer, Model LB-2) constant between 35 and 40 torr. Arterial blood P_{O_2}, P_{CO_2}, and *p*H determinations were made prior to, during, and after AV conduction measure-

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Received from the Department of Anesthesiology, University of Wisconsin Medical School, Madison, Wisconsin 53706. Accepted for publication June 16, 1977. Supported in part by Grant #135 4433, funded from the University of Wisconsin Graduate School, the Wisconsin Heart Association (Grant-in-Aid), and the H. G. Barsumian, M.D., Memorial Fund. Presented in part at the Annual Meeting of the Federation of American Societies for Experimental Biology, Anaheim, California, April 1976, and at the Annual Meeting of the American Society of Anesthesiologists, San Francisco, California, October 1976.

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ments at each anesthetic concentration. Arterial blood *p*H was adjusted to 7.40 ± 0.03 as necessary by iv administration of sodium bicarbonate. End-tidal enflurane concentrations were maintained within 10 per cent of the desired levels for at least 10 minutes prior to and for the duration of AV conduction measurements. An infrared lamp or an intravenous infusion of cold physiologic saline solution was used as necessary to keep animals normothermic (37 C). The duration of each experiment was less than four hours.

The effects of enflurane on AV conduction times were studied at each concentration in spontaneously beating hearts (18 dogs), and during incremental atrial pacing (13 dogs). AV nodal, His–Purkinje, and ventricular conduction times were evaluated. In addition, the effects of enflurane and of changes in basic paced heart rate on the effective refractory period of the atrium, the functional refractory period of the AV node, and AV nodal conductivity[14] were evaluated in those ten of the 18 dogs whose hearts could be paced at basic rates of 120 and 200 beats/min. Our techniques for recording surface and His-bundle electrocardiograms and for high right atrial pacing have been described elsewhere.[11] His-bundle, surface, and high right atrial electrograms and arterial blood pressure (femoral artery, Statham P23Db) or voice input were continuously recorded (Tandberg Instrumentation Series 100) for later playback and data analysis. Mean arterial blood pressures at MAC 1.0, 1.5, and 2.0 were 100 ± 14, 76 ± 15, and 66 ± 16 torr.

Atrioventricular conduction times, heart rate, and

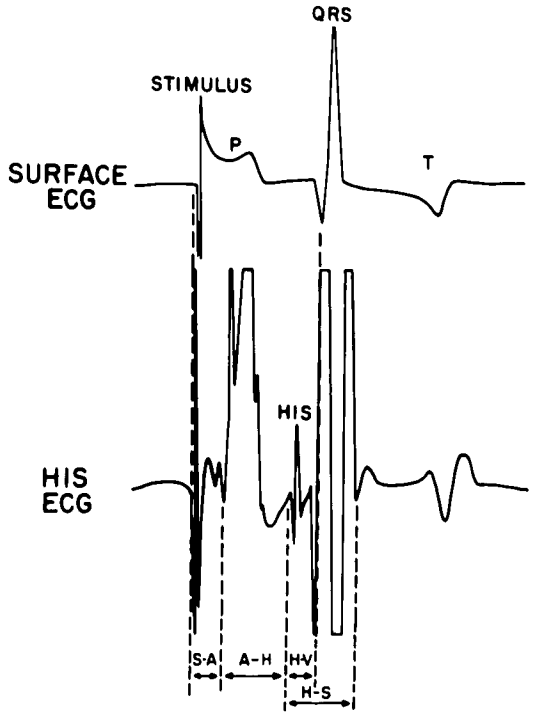

FIG. 1. Tracing from record of one experiment. The upper recording is Lead II of the surface ECG. The lower recording is the His bundle electrogram (HBE). The S-A interval (atrial conduction time) is measured from the stimulus artifact to the onset of the rapid deflection of low atrial activity in the HBE. The A-H interval (AV nodal conduction time) is measured from the onset of low atrial activity to the beginning of the His potential. The H-V interval (His-Purkinje conduction time) is measured from the His potential to the upstroke of the R wave in the QRS complex of the surface ECG. The H-S interval (ventricular conduction time) is measured from the His potential to the end of rapid ventricular activity in the HBE.

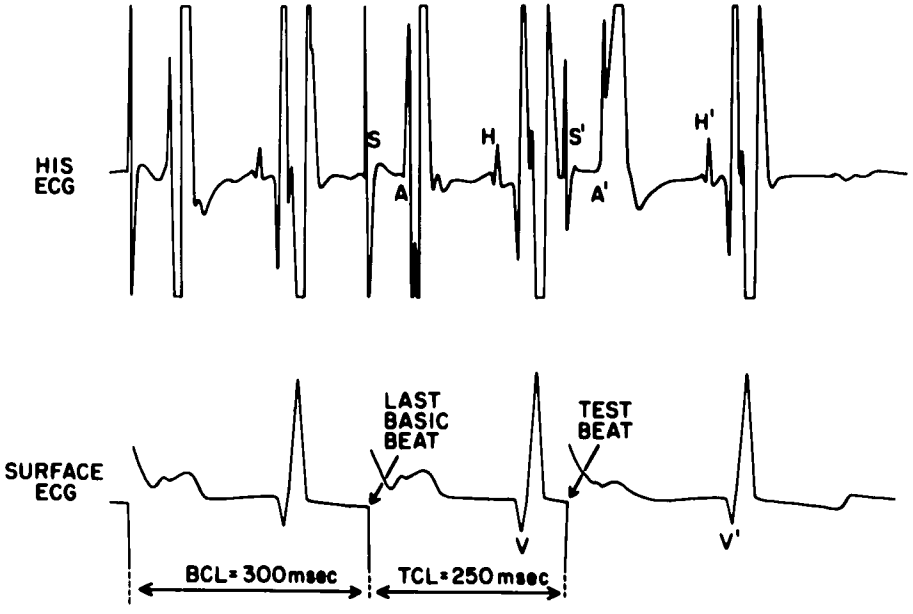

FIG. 2. Tracing from record of one experiment. Refractory period and conductivity measurements. The upper recording is Lead II of the surface ECG. The lower recording is the His-bundle electrogram. S, A, H and V denote the beginning of the stimulus artifact, low atrial activity, His potential, and ventricular activity in the last of a series of basic beats (basic cycle length = 300 msec). S', A', H', and V' denote activity from the same sites in the test beat (test cycle length = 250 msec). Intervals measured for refractory period determinations and conductivity measurements are discussed in the text.

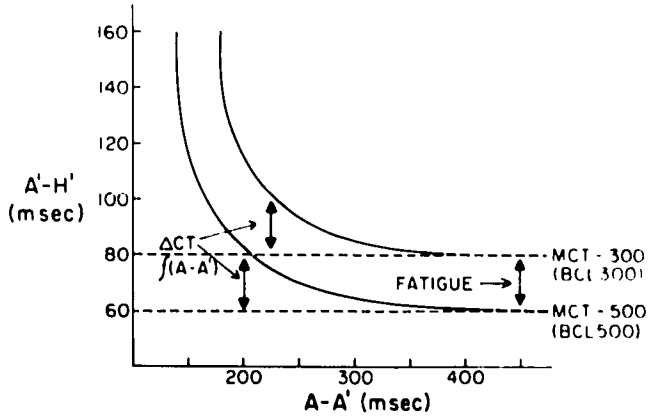

FIG. 3. AV nodal conductivity. Schematic showing the AV nodal conduction time of test beat (A'–H', ordinate) as function of atrial coupling interval (A–A', abscissa). Minimum AV nodal conduction time (MCT), fatigue, and interval-related conductivity (ΔCT) are defined in the text.

the time intervals required for measuring refractory periods and AV nodal conductivity were calculated using a programmable, digital calculating oscilloscope (Norland Instruments 2001). Cursors were positioned on the desired complexes and the time differences between the two points calculated and displayed on the oscilloscope screen. Permanent records of signals displayed on the oscilloscope were made with an X, Y plotter (Hewlett-Packard, HP7004B).

Atrioventricular conduction intervals measured during spontaneous heart rate and incremental atrial pacing are depicted in figure 1. These included:

1) S–A (atrial conduction time): stimulus artifact to onset of rapid deflection of the low atrial potential in the His-bundle electrogram (HBE).

2) A–H (AV nodal conduction time): onset of rapid deflection of low atrial potential in the HBE to the beginning of the His potential in the HBE.

3) H–V (His–Purkinje conduction time): beginning of His-bundle potential (HBE) to upstroke of R wave in the simultaneously recorded surface ECG, Lead II.

4) H–S (ventricular conduction time): beginning of His-bundle potential (HBE) to end of rapid ventricular activity in the HBE.

Incremental atrial pacing over a range of heart rates from 120 to 200 beats/min (paced cycle lengths decreased from 500 to 300 msec by 25-msec decrements) was used to detect anesthetic effects on the slope or intercept of the linear relationship between AV conduction time and heart rate.[9,10] An atrial extrastimulus method was used to detect anesthetic effects on AV nodal conductivity[14] and refractory periods. Extrastimuli were delivered at various cycle lengths (test cycle length) during atrial pacing at 120 or 200 beats/min (basic cycle length = 500 or 300 msec). Test cycle lengths were decreased from 550 msec as follows: 500, 450, 400, 350, 325, 300, 290, 280 . . . 250, 245 . . . and thereafter by 5-msec amounts until atrial effective refractoriness was encountered. A more accurate estimate of the atrial effective refractory period was provided by determining to the nearest 1 msec the reduction in test cycle length necessary for failure of atrial impulse propagation.

Time intervals used for refractory period and conductivity measurements were defined as follows (fig. 2):

1) Atrial coupling interval: Time interval between low atrial complexes in the His-bundle electrogram of the last of a series of basic (A) and the test (A') beats.

2) His coupling interval: Time interval between His complexes of the last of a series of basic (H) and the test (H') beats.

3) AV nodal conduction time, test beat: Time interval between low atrial (A') and His (H') activity of the test beat.

The atrial effective refractory period was the longest test beat cycle length that failed to result in atrial capture. The functional refractory period of the AV node was the shortest H–H' interval propagated to the ventricles. AV nodal conductivity was assessed by measurements of its minimum conduction time, fatigue, and interval-related conductivity (fig. 3):

1) Minimum AV nodal conduction time (MCT–AV node): A'–H' interval of test beat (cycle length = 500 msec) at a basic cycle length of 500 msec (MCT-500) or 300 msec (MCT-300).

2) Fatigue: Difference in msec between MCT-500 and MCT-300, or change in MCT-AV node related to increase in basic atrial paced rate.

TABLE 1. Effect of Enflurane on AV Conduction Intervals: Spontaneous Heart Rate (Mean ± 1 SD, 18 Dogs)

	HR (Beats/Min)	A–H (msec)	H–V (msec)	H–S (msec)
MAC 1.0	118.2 (± 15.6)	72.9 (± 12.9)	36.8 (± 3.7)	95.1 (±13.4)
MAC 1.5	112.5* (± 11.2)	77.7* (± 14.8)	36.2 (± 3.2)	91.9 (± 9.1)
MAC 2.0	111.5* (± 10.8)	77.5* (± 14.7)	37.1 (± 3.7)	94.4 (± 9.7)

* $P < 0.5$ compared with 1.0 MAC value.

3) Interval-related conductivity (ΔCT): Difference in msec between MCT-500 or MCT-300 and the A′–H′ interval for test beats (cycle length < 500 msec).

Student's t test was used to compare the effects of each enflurane concentration on heart rate and AV conduction intervals (spontaneously beating hearts), and refractory periods and minimum AV nodal conduction time (paced hearts). Enflurane effects on AV conduction intervals during incremental atrial pacing were compared using a multiple linear regression model.‡ The rationale for choosing this model is similar to that presented earlier.[10] Enflurane and basic cycle length effects on interval-related conductivity were evaluated by constructing a multiple linear regression model‡ for the relationship between log ΔCT for values of ΔCT > 10 msec (ordinate) and A–A′ intervals between 200 and 400 msec (abscissa). In both models anesthetic and basic cycle length (interval conductivity only) effects were accounted for by assigning independent intercept (A) and slope (B) coefficients. Coefficients were dropped from the model (assigned a value of 0) when not significant ($P < 0.05$) by t test.

‡ See NAPS Document No. 03158 for 8 pages of supplementary materials which describe the models used for determining anesthetic and basic cycle length effects on A-V conduction. Predicted slope and intercept coefficients for the models are also included. Order from ASIS/NAPS, Microfiche Publications, P.O. Box 3513, Grant Central Station, New York, New York 10017. Remit in advance for each NAPS accession number. Institutions and organizations may use purchase orders when ordering; however, there is a billing charge for this service. Make checks payable to Microfiche Publications. Photocopies are $5.00. Microfiche are $3.00 each. Outside the United States and Canada, postage is $3.00 for a photocopy or $1.00 for a fiche.

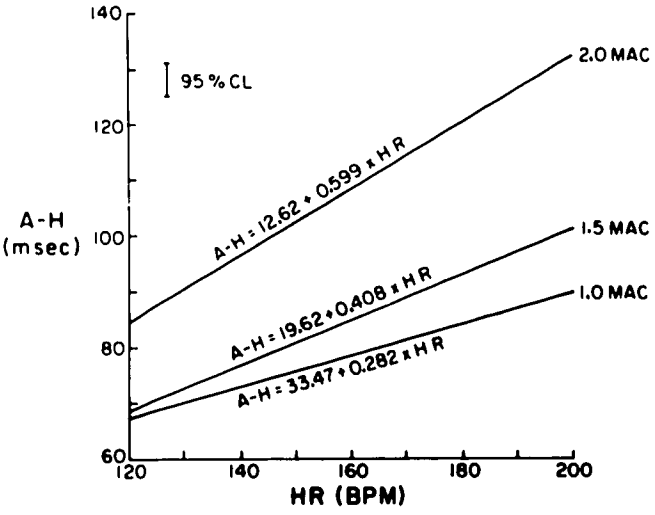

FIG. 4. Enflurane: A–H *vs.* heart rate. AV nodal conduction time. Incremental atrial pacing. Predicted A–H intervals for heart rates between 120 and 200 beats/min. Effects of enflurane, 1.0, 1.5, and 2.0 MAC, on the rate-dependence of AV nodal conduction time. Data from 13 experiments. Correlation coefficient = 0.937.

TABLE 2. Effects of Enflurane on the Functional Refractory Period of the AV Node and Effective Refractory Period of the Atrium for Basic Cycle Lengths of 500 and 300 msec (Mean ± 1 SD, 10 Dogs)

	MAC		
	1.0	1.5	2.0
Functional refractory period of AV node (msec)			
At basic cycle length 300 msec	236.3 (± 12.7)	252.9† (± 13.5)	265.4† (± 18.3)
At basic cycle length 500 msec	263.3* (± 18.0)	273.9*† (± 15.1)	285.4*† (± 21.0)
Effective refractory period of atrium (msec)			
At basic cycle length 300 msec	116.1 (± 9.8)	157.8† (± 39.9)	179.3† (± 45.7)
At basic cycle length 500 msec	133.4* (± 15.7)	156.6† (± 30.0)	168.0† (± 36.5)

* $P < 0.05$ compared with value for basic cycle length = 300 msec, same MAC.

† $P < 0.05$ compared with value for MAC 1.0, same basic cycle length.

Results

Enflurane produced a decrease in heart rate and a prolongation in AV nodal conduction time with no change in either His–Purkinje or ventricular conduction times as its concentration was increased in spontaneously beating hearts (table 1).

During incremental increases in atrial paced rate,

TABLE 3. Enflurane Effects on Minimum AV Nodal Conduction Time at Basic Cycle Lengths of 500 and 300 msec (Mean ± 1 SD, 10 Dogs)

	MAC		
	1.0	1.5	2.0
Minimum AV nodal conduction time (msec)			
At basic cycle length 500 msec	72.4 (± 14.1)	75.5 (± 14.2)	82.1* (± 13.4)
At basic cycle length 300 msec	72.9 (± 9.3)	80.5* (± 14.0)	88.0*† (± 10.4)

* $P < 0.05$ compared with value for 1.0 MAC, same basic cycle length.

† $P < 0.05$ compared with value for 500 msec, same basic cycle length.

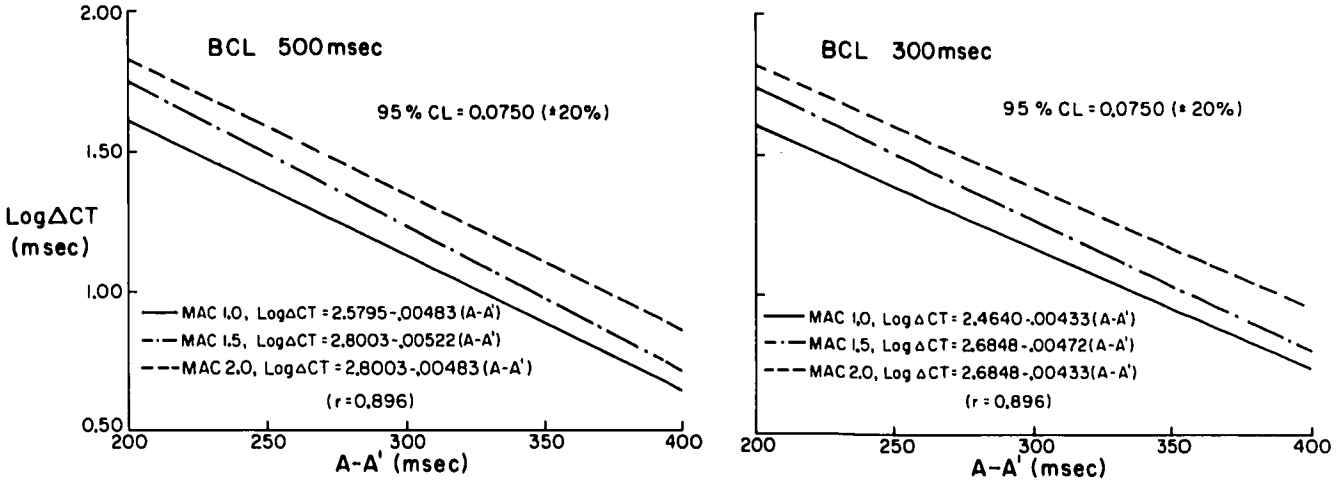

FIG. 5. Interval conductivity: effect of enflurane on the relationship between log ΔCT and prematurity of the test beat (A–A' interval). Data from ten experiments. Correlation coefficient = 0.948.

enflurane enhanced the rate dependence of AV nodal conduction time (fig. 4). There was no effect of paced heart rate or enflurane on His–Purkinje or ventricular conduction times.

Enflurane prolonged both the atrial effective refractory period and the functional refractory period of the AV node (table 2). Enflurane also prolonged minimum AV nodal conduction time at both basic paced atrial rates; however, fatigue was significant only at MAC 2.0 (table 3).

Enflurane increased interval-related conductivity for A–A' intervals between 200 and 400 msec as its concentration increased (fig. 5).

Discussion

These results indicate that enflurane prolongs AV nodal conduction time both in spontaneously beating hearts and during incremental increases in atrial paced rate, as shown for halothane in our earlier studies.[9–11] In contrast to halothane,[9–11] enflurane did not prolong His–Purkinje or ventricular conduction time within the range of MAC levels evaluated. If such differences between halothane and enflurane are important in ventricular arrhythmogenesis (*e.g.*, those arrhythmias caused by re-entry of excitation[8]), our observations may explain in part the clinical impression that ventricular arrhythmias are less likely to occur during enflurane than during halothane anesthesia.

Technical differences between this and our earlier study of halothane effects on refractory periods and AV nodal conductivity[11] preclude a strict comparison of the effects of enflurane and halothane on these variables. However, we consider anesthetic and other drug effects on the conduction characteristics of atrial extrasystoles through the AV node determined by measurements of its conductivity to bear an important relationship to the mechanism of supraventricular arrhythmias caused by re-entry of excitation. Re-entry requires slowed conduction, unidirectional block, and a pathway so that the potentially re-entrant impulse can gain access to the conduction system before the arrival of the next normal impulse from above. Presumably, re-entry can occur whereever (atria, AV node) these conditions are met. We cannot at this time relate the effects of enflurane, or apparent differences between them and effects halothane on AV nodal conductivity, to supraventricular arrhythmogenesis. Studies comparable to this one to determine the effects of other anesthetics and drugs are in progress to delineate these differences further and assess their importance.

The authors thank Carol Sakowski and Carol Malkinson for technical assistance, the Ohio Chemical Company for generously supplying enflurane (Ethrane), and Dr. Brian Joiner and Warren Lamboy of the University of Wisconsin Statistical Consulting Laboratory for their professional assistance.

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