Reducing VNS stimulation parameters: Is it safe?

É seguro reduzir parâmetros de estimulação do VNS?

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Abstract

Introduction Vagal nerve stimulation (VNS) is an adjuvant therapy used in the treatment of patients with refractory epilepsy who are not candidates for resective surgery or who have limited results after surgical procedures. Currently, there is enough evidence to support its use in patients with various types of epilepsy. Therefore, the present study was conducted to explore the possibility of optimizing therapy by reducing the consumption of the system's battery.

Methods The prospective and double-blind analysis consisted in the evaluation of 6 patients submitted to VNS implantation for 3 months, followed by adjustment of the stimulation settings and continuity of follow-up for another month. The standard protocol was replaced by another with a frequency value of 20 Hz instead of 30 Hz to increase battery life. The safety of this procedure was evaluated through the assessment of two main variables: seizures and side effects.

Results The stimulation at 20 Hz showed 68% reduction in the incidence of seizures ($p = 0.054$) as well as low incidence of side effects.

Conclusion The present study suggests that the reduction of the stimulation frequency from 30 to 20 Hz is a safe procedure, and it does not compromise the effectiveness of therapy.

Keywords
► vagus nerve stimulation
► vagal stimulation
► VNS
► refractory epilepsy

Resumo

Introdução A estimulação do nervo vagal (VNS, na sigla em inglês) é uma terapia adjuvante usada no tratamento de pacientes com epilepsia refratária que não são candidatos à cirurgia de ressecção ou que apresentam resultados limitados após procedimentos cirúrgicos. Atualmente, há evidências suficientes para apoiar seu uso em pacientes com vários tipos de epilepsia. Portanto, este estudo foi realizado para explorar a possibilidade de otimizar a terapia reduzindo o consumo da bateria do sistema.

Métodos A análise prospectiva e duplo-cega consistiu na avaliação de 6 pacientes submetidos ao implante de VNS por 3 meses, seguido de ajuste das configurações de

Palavras-chave
► estimulação do nervo vago
► estimulação elétrica
► nervo vago
► epilepsia resistente à medicamentos

estimulação e continuidade do seguimento por mais 1 mês. O protocolo padrão foi substituído por outro com um valor de frequência de 20 Hz em vez de 30 Hz para aumentar a vida útil da bateria. A segurança desse procedimento foi avaliada através da avaliação de duas variáveis principais: crises convulsivas e efeitos colaterais.

Resultados   A estimulação em 20 Hz apresentou redução de 68% na incidência de convulsões ($p = 0,054$), bem como baixa incidência de efeitos colaterais.

Conclusão   Este estudo sugere que a redução da frequência de estimulação de 30 para 20 Hz é um procedimento seguro e não compromete a eficácia da terapia.

Introduction

One of the techniques used in the treatment of patients with refractory epilepsy that are not candidates for resective surgery is vagus nerve electrical stimulation (VNS).[1,2] This technique consists of implanting a bipolar electrode in the vagus nerve in the cervical region and a generator in the infraclavicular region. The left side is the chosen one for this procedure due to the cardiac fibers that originate from the right vagus nerve. Although the mechanism of action by which it operates has not yet been fully elucidated, it is believed to involve diffuse effects on brain metabolism from both cortical and subcortical regions, through modulation of the activity of the *locus ceruleus*, nucleus of the solitary tract and reticular formation of the brain stem.[3] Results show that this therapy is effective not only in reducing the frequency and duration of epileptic seizures,[4–6] but also in promoting a better quality of life for these patients.[7]

Mechanism of Action

It is postulated that the cortical modulation exerted by VNS is manifested through the modulation of the noradrenergic and serotonergic systems, especially due to stimulation of the *locus ceruleus* and the dorsal raphe nuclei, which was confirmed through measurement of monoamines in cerebrospinal fluid (CSF).[8] It is known that the increase of the activity of the *locus ceruleus* after electrical stimulation of the vagus nerve, demonstrated by an increase in c-fos, can cause both release of norepinephrine in the limbic circuit as well as activation of the dorsal raphe nuclei, which send diffuse serotonergic projections to the telencephalon and diencephalon.[9]

Anatomy

The vagus (X) nerve is a mixed cranial nerve with ~ 80% of sensitive fibers. Efferent fibers innervate the larynx and promote parasympathetic control of the heart, lungs, and abdominal viscera. It exits the brainstem at the posterolateral sulcus of the medulla with the glossopharyngeal (IX) and accessory (XI) nerves.[10] The right vagus nerve innervates the sinoatrial node while the left innervates the atrioventricular node. The ideal nerve location for VNS implantation is the cervical region, where it travels in the carotid sheath, between the carotid artery and the jugular vein. A segment of ~ 3 cm is commonly needed for implantation and, when feasible, it should be performed as distal as possible in case a new electrode is needed in the future.

Surgical Procedure

As described earlier, the device is preferentially implanted on the left side of the patient to avoid the cardiac fibers of the right vagus nerve. The electrode and generator are tested before the procedure. The first surgeon is at the patient's left in the cervical region. The patient lies supine on the surgical table with the head supported by a cushion and slightly extended; a pad is placed under the shoulder for assistance.

A 5-cm longitudinal incision is made at the level of the cricothyroid interval from the midline to the anterior border of the sternocleidomastoid muscle (►**Fig. 1**). The platysma muscle is divided in the direction of the fibers, and the deep cervical fascia is opened. The sternocleidomastoid muscle is folded laterally to expose the neurovascular bundle through blunt dissection. The carotid sheath is opened to expose the carotid artery and the jugular vein, which is retracted laterally to reveal the vagus nerve trunk deep in between structures (►**Fig. 2**). After careful dissection, the lead's spirals are wrapped around the nerve from the proximal to the distal contact (►**Fig. 3**). It is of great importance to maintain the adequate position of spirals (the anchor tether

Fig. 1 A 5cm longitudinal incision is made at the level of the cricothyroid interval from the midline to the anterior border of the sternocleidomastoid muscle
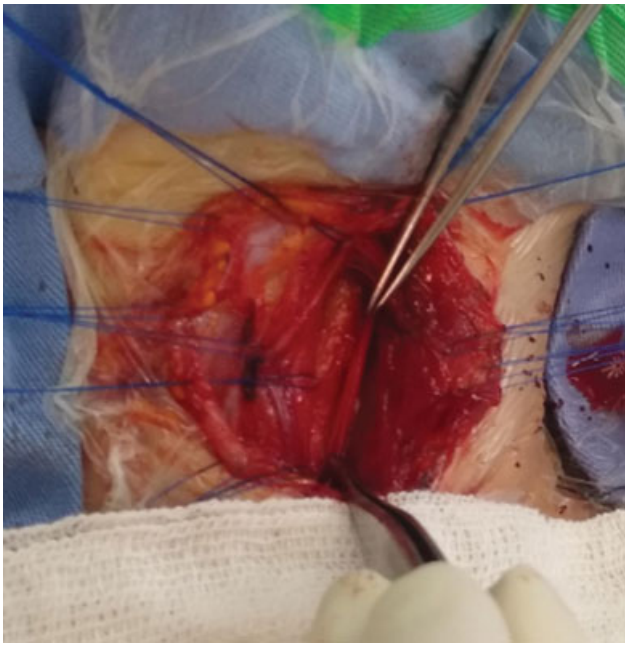
Fig. 2 The carotid sheath is opened to expose the carotid artery and the jugular vein, which is retracted laterally to reveal the vagus nerve trunk deep in between structures

Fig. 3 After careful dissection, the lead's spirals are wrapped around the nerve from the proximal to the distal contact

is placed inferiorly; the positive contact in between; and the negative contact superiorly, as demonstrated in ►**Fig. 4**) to stimulate afferent and non-efferent fibers.

To place the generator on the anterior chest wall inferior to the clavicle, an incision is made at the level of the anterior axillary line to create a subcutaneous pouch under the pectoral fascia, large enough to accommodate the device (►**Fig. 1**). The electrode is then carefully tunneled from the neck to the chest, above the sternocleidomastoid muscle and the clavicle, and connected to the generator. The intraoperative test is performed to confirm adequate system functioning through impedance testing. If the implanted generator supports closed-loop stimulation, it is also necessary to verify the system's capability of correctly identifying the heart rate. At our center, stimulation is initiated immediately after the
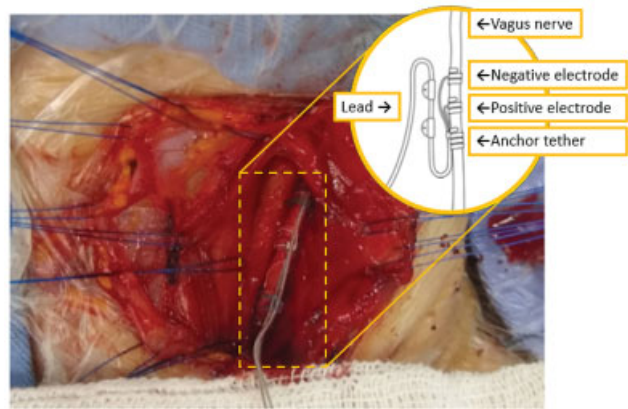
Fig. 4 Adequate position of spirals (anchor tether is placed inferiorly, positive contact, in between, and negative contact, superiorly)

procedure with the following settings: 0.25 to 0.5 mA, 30 Hz, 500 micros, 30 seconds ON, and 5 minutes OFF.

Rationale

The device employed for the electrical stimulation of the vagus nerve allows adjustment of several parameters, as current, frequency, pulse width, ON and OFF time. Although the current stimulation protocol was initially based on animal studies[11–13] and, subsequently, on humans (mainly in EOS 1–5 studies), it has not yet been thoroughly elucidated and individual variations are quite frequent,[14] mainly due to the lack of conclusive randomized trials objectively comparing different values of frequency, amplitude, and pulse width. Therefore, the present study intends to demonstrate the safety of reducing the stimulation frequency from 30 to 20 Hz.

Methods

The current study consisted in a double-blind prospective analysis of patients with refractory epilepsy previously submitted to VNS implantation who underwent reduction of frequency stimulation (from 30–20 Hz) and were followed up for evaluation of changes in frequency and/or duration of epileptic seizures and emergence of side effects.

The eligibility criteria included individuals of both genders from 2 to 18 years of age, with refractory epilepsy of focal or generalized origin, already submitted to VNS implantation at Hospital Pequeno Príncipe by the same surgeon (T. O.), that demonstrated interest in participating voluntarily. The exclusion criteria, in turn, consisted of age group outside the previously mentioned range or lack of interest in participating in the research. The project was approved by the ethics committee of Hospital Pequeno Príncipe and did not generated expenses for the participants. All individuals who agreed to participate in the survey signed the informed consent. It was clarified that there could be a reduction in the number of surgical procedures for generator replacement due to increase in battery survival. All changes in stimulation parameters were performed in the hospital, and the patient remained in place long enough for at least two cycles of stimulation to occur to early diagnose any immediate side
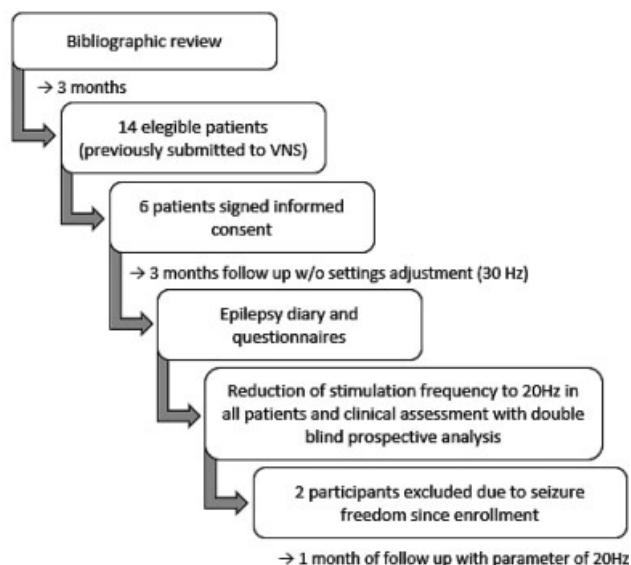
Fig. 5 Methods' flowchart

effects. It should be noted that the researcher responsible for setting adjustments was not the same who evaluated the results. The participants and their families were extensively instructed on the double-blind nature of the project and the need for randomization to reduce placebo effect.

Six patients stimulated with 30 Hz were initially followed up for 3 months with a questionnaire and a seizure diary. Due to lack of participant compliance, the authors opted for collecting data through online diaries, telephone contacts or office visits. After baseline evaluation, the frequency stimulation was reduced to 20 Hz, and the patients were followed up for another month. Because of the small sample size, adjustments were performed for all patients, which composed the control group. However, to maintain the double-blind approach, the participants, and the author responsible for evaluating the results were unaware of this information (►**Fig. 5**).

In addition to a comparative statistical analysis performed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA), the data were processed through the *t*-paired analysis in the Minitab program (Minitab, LLC., State College, PA, USA) to compare the two stimulation groups (20 and 30 Hz). To test the normality of the distribution of the 30 Hz and 20 Hz samples according to the multiple variables, the Anderson-Darling and Ryan-Joiner were used. The H0 hypothesis, rejected if $p < 0.05$ for 95% confidence intervals, considered that the sample distribution followed a normal distribution.

Results

Of the 14 patients selected for the research, only 6 demonstrated interest in participating and signed the informed consent. The mean age of the sample analyzed was 10 years (8–18 years) and half of the participants was female. In the baseline evaluation, two patients had already presented with complete seizure remission. An average of 109 seizures per week per patient was observed, with 90.7% being partial, $\sim 9\%$ drop-attack, and 0.3% being tonic-clonic. All patients who were still seizing

obtained some reduction in seizure duration, and 75% were considered responsive (achieved more than 50% reduction in seizure frequency). Likewise, three of four patients reported less intense events, while one remained unchanged.

With the inclusion of all patients in the group of 20 Hz, however, it was not possible to exclude the possibility that the data did not follow a normal distribution. This probably occurred due to the presence of two outliers that no longer had seizures since the baseline evaluation and stayed that way after reducing the frequency to 20 Hz. To approach normality, it was decided to exclude these two participants and perform all the analysis with only the data of the four remaining ones.

Two patients reported side effects after frequency reduction to 20 Hz: one had transient dysphonia while the second evolved with permanent dysphagia and dysphonia. Nonetheless, it is crucial to mention the latter had clinical deterioration due to hospitalization, which could have contributed to the complaints.

Contrarily to expectations, in the month following settings adjustment, there was a 68% reduction in seizures ($p = 0.054$). Moreover, in the 75% of patients who were still seizing, a reduction in both intensity and duration of the episodes was noticed. It is necessary to emphasize that, in the two patients who had no seizures, there was no clinical worsening after reducing the frequency to 20 Hz.

After comparing the mean of the total number of seizures during stimulation at 30 Hz and at 20 Hz, there was no statistically significant difference ($p = 0.054$), despite a tendency of seizure reduction with 20 Hz stimulation. This fact can be explained by the presence of overlap data in the histogram of the two distributions, even though the means of total seizure number with stimulation at 30 Hz and at 20 Hz were distinct (**Graph 1**). When applying the paired *t*-test, it was not possible to state with 95% confidence that the averages of the total seizure number with stimulation at 30 Hz or 20 Hz were different since the confidence interval included 0 (- 4.0; 227.5), as demonstrated in ►**Table 1**. However, when changing the interval (26.1; 197.4), it became evident that the averages differed with 90% certainty (►**Table 2**). This should be carefully interpreted, however, as the resultant seizure reduction could be simply a
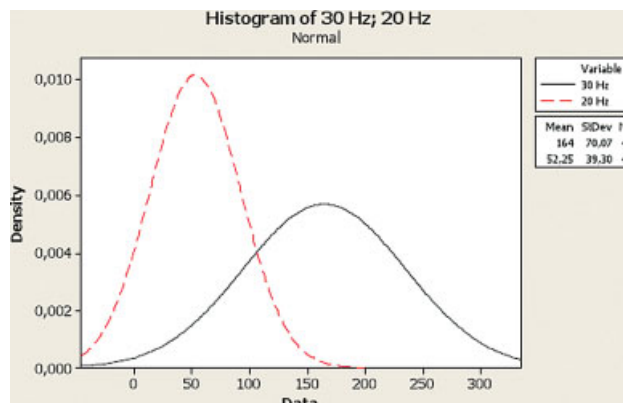
Graph 1 Histogram of the total number of seizures during stimulation at 30Hz and at 20Hz

Table 1 Paired *t*-test of the total number of seizures with stimulation at 30 and 20 Hz

	N	Mean	Standard deviation	Standard error
30 Hz	4	164	70.1	35
20 Hz	4	52.3	39.3	19.6
Difference	4	111.8	72.7	36.4

95% confidence interval for the mean difference: (- 4.0; 227.5).
T-test of difference from mean = 0 (versus no = 0); *t*-value = 3.07; *p*-value = 0.054.

Table 2 Paired *t*-test of the total number of seizures with stimulation at 30 and 20 Hz

	N	Mean	Standard deviation	Standard error
30 Hz	4	164	70.1	35
20 Hz	4	52.3	39.3	19.6
Difference	4	111.8	72.7	36.4

90% confidence interval for the mean difference: (26.1; 197.4).
T-test of difference from mean = 0 (versus no = 0); *t*-value = 3.07; *p*-value = 0.054.

consequence of the stimulation of the vagus nerve itself and could appear months after the initiation of therapy.

Discussion

The VNS system allows for changes in almost all settings, and most of the patients are stimulated with the standard protocol of 30 Hz, 500 µs, 30 seconds ON, 5 minutes OFF, and amplitudes that vary from 0.25 to 2.25 mA.

Frequency values range from 20 to 30 Hz, because it has been demonstrated that frequencies greater than 50 Hz could cause irreversible nerve damage.[15] A recent study in rats, however, suggested that frequencies between 130 Hz to 180 Hz as recommended in brain, spinal cord, and trigeminal stimulation, could lead to greater seizure attenuation than 30 Hz stimulation.[16] Nonetheless, these results have not yet been demonstrated in humans. Low frequency electrical stimulation (1 Hz), in turn, has not been as effective as high frequency (30 Hz) in seizure control.[17]

Diversely, pulse width ranges from 250 to 500 µs, and current amplitude from 0.0 up to 3.5 mA. The amplitude chosen for initial stimulation, however, varies from 0.25 to 0.5 mA and is gradually increased to 1.75/2 mA in months. Most patients do not benefit from further increases as the vast majority of fibers are already stimulated with values close to 1.5 to 2.25 mA.[18] Although it has been shown that clinical response with a reduction in epileptic seizures in the first 3 months after implantation was quite similar in groups that used current amplitudes lower or higher than 1 mA,[19] it should be noted that in the non-responsive group there was greater improvement after increasing the amplitude. This fact could be explained not only by settings adjustment, but also by the stimulation time itself,[9] since clinical response may be delayed on account of the cumulative effect of stimulation. Furthermore, as children tolerate increases in amplitude better than adults because of fewer side effects, a need for higher current or pulse width values in these patients may be noticed.[20]

It is noteworthy that stimulation does not occur continuously, but rather in cycles. Although the initial stimulation is generally started with cycles of 30 seconds ON and 5 minutes OFF, the system allows for cycles of 7 to 60 seconds ON and 0.2 to 10 minutes OFF. In a retrospective analysis of the parameters of electrical stimulation in 154 patients in the XE5 study, it was not possible to correlate seizure control with changes in current amplitude, frequency, and pulse width between 3 and 12 months of follow-up. In one group, however, it was observed that reducing the OFF time to $\leq$ 1.1 minute led to better control with the reduction in seizures being improved from 21 to 39%.[21] Although some authors advocate rapid electrical stimulation (7 seconds ON and 30 seconds OFF), it has not yet been possible to demonstrate statistical difference with this protocol.[4]

Moreover, it should be considered that increases in electrical stimulation parameters will generate higher battery consumption and a consequent reduction in battery life,[18] in addition to increases in surgical procedures to replace the generator. For example, computational models have already demonstrated that, although there are less stimulated fibers with pulse width reduction from 500 to 250 µs, the required increase in amplitude to maintain the same electrical stimulation consumes less energy than with 500 µs pulse width stimulation and lower amplitudes.[18] Lower values of pulse width (250 µs) and frequency (20 Hz) can be used on patients according to the manufacturer's manual (Cyberonics, 2015, VNS Therapy®, Cyberonics Inc. Houston TX, USA), with the main objective of reducing side effects. A projection of battery life according to the various current values, pulse width, and frequency can be seen in ►**Fig. 6**.

The reduction from 30 to 20 Hz in the present study showed a reduction of 68% in the incidence of seizures (*p* = 0.054) as well as low incidence of permanent side effects (only 1 out of 6 patients). However, it is necessary to interpret these data with caution since most of the participants were the ones who responded to therapy. Moreover, this improvement could also result from the time patients had been treated, as vagus nerve electrical stimulation response may not be immediate, and its effectiveness may progressively increase over time.

Limitations

The main limitations of our study are the small sample size and the use of the same patient as his own control group. The next step in the investigation of vagus nerve electrical stimulation at 20 Hz frequency would be the development of a randomized study, with a group of stimulation at 20 Hz and a control group at 30 Hz with crossover after a follow-up period.

Parameters at 3kOhms (M103/104)			Time from BOL* to IFI			Time from IFI to N EOS			Time from N EOS to EOS		
			10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
mA	Hz	µS	Years	Years	Years	Years	Years	Years	Years	Years	Years
0.5	10	130	>10	>10	>10	2.8	2.5	2.4	2.2.	2.0	1.9
0.5	15	130	>10	>10	>10	2.7	2.2	1.9	2.1	1.7	1.5
0.5	20	130	>10	>10	>10	2.5	1.9	1.7	2.0	1.5	1.3
0.5	25	130	>10	>10	>10	2.4	1.7	1.4	1.9	1.4	1.2
0.5	30	130	>10	>10	9.5	2.3	1.6	1.3	1.8	1.3	1.1
0.5	10	250	>10	>10	>10	2.7	2.3	2.0	2.1	1.8	1.6
0.5	15	250	>10	>10	>10	2.5	1.9	1.6	2.0	1.5	1.3
0.5	20	250	>10	>10	>10	2.4	1.7	1.4	1.9	1.3	1.1
0.5	25	250	>10	>10	8.7	2.3	1.5	1.2	1.8	1.2	0.9
0.5	30	250	>10	9.8	7.6	2.1	1.3	1.0	1.7	1.0	0.8
0.5	10	500	>10	>10	>10	2.5	1.9	1.6	1.9	1.5	1.2
0.5	15	500	>10	>10	8.9	2.3	1.5	1.2	1.8	1.2	0.9
0.5	20	500	>10	9.3	7.2	2.1	1.2	1.0	1.6	1.0	0.8
0.5	25	500	>10	8.1	6.1	1.9	1.1	0.8	1.5	0.9	0.6
0.5	30	500	>10	7.1	5.2	1.8	0.9	0.7	1.4	0.8	0.6
0.5	10	750	>10	>10	9.4	2.3	1.6	1.3	1.8	1.2	1.0
0.5	15	750	>10	9.1	7.0	2.1	1.2	0.9	1.6	1.0	0.7
0.5	20	750	>10	7.5	5.6	1.9	1.0	0.7	1.5	0.8	0.6
0.5	25	750	>10	6.4	4.7	1.7	0.9	0.6	1.3	0.7	0.5
0.5	30	750	>10	5.5	4.0	1.5	0.7	0.5	1.2	0.6	0.4
0.5	10	1000	>10	>10	7.9	2.2	1.4	1.1	1.7	1.1	0.8
0.5	15	1000	>10	7.7	5.8	1.9	1.0	0.8	1.5	0.8	0.6
0.5	20	1000	>10	6.3	4.5	1.7	0.8	0.6	1.3	0.7	0.5

Fig. 6 Projection of battery life according to the various current values, pulse width, and frequency

Conclusions

When considering the significant reduction in the frequency of epileptic seizures and the improvement in the quality of life of implanted patients, along with the low incidence of irreversible or debilitating side effects, it is possible to recognize that electrical stimulation of the vagus nerve is a safe therapy in the treatment of pediatric and adult patients with refractory epilepsy who are not candidates for resective surgery. Although this was a pilot study with a small sample size, it demonstrated that, in the short term, it is apparently safe to reduce the stimulation frequency to 20 Hz without compromising the effectiveness of therapy. The subsequent increase in battery lifetime would, consequently, reduce the need of surgical replacements of the generator.

Conflict of Interests
The authors have no conflict of interests to declare.

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