Modification of Sinus Node Function by Epicardial Laser Irradiation in Dogs

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This study tested the feasibility of neodymium:YAG laser photocoagulation of selected sinus node areas to depress sinus rate responsiveness. In 14 open-chest dogs, origin of the sinus impulse (O point) was electrically mapped from the epicardium before and during isoproterenol infusion. Epicardial laser photocoagulation was applied to the O point observed during isoproterenol infusion and stepwise to remapped new O points until a 30±5% decrease in heart rate occurred. Long-term effects were assessed by Holter monitoring and electropharmacologic testing preoperatively and up to 10 weeks or 6 months. Mean (±SEM) percent decreases were observed at 10 weeks in the following parameters: average 24-hour heart rate, 17.4±5.0%; maximum heart rate on Holter, 30.5±3.5%; heart rate during pharmacologic autonomic blockade, 32.7±3.5%; and maximum heart rate on isoproterenol, 23.1±4.6% (all p<0.01). Curves with pacemaker recovery time plotted against control cycle length remained unchanged. Holter monitoring did not show excessive bradycardic episodes even after administration of propranolol. In three control dogs (sham operation), sinus node function remained unchanged. Histologic study of the irradiated area showed replacement by inflammatory cells, fibrosis, and cartilage formation with surrounding normal cells and occasional cells resembling pacemaker-like cells at the caudal end of the sinoatrial node. This study suggests that 1) map-guided graded laser photocoagulation of sinus node regions showing earliest activation during catecholamine stimulation successfully limits maximum heart rates without causing significant bradycardia, 2) the effects are long lasting, and 3) the remaining pacemaker behaves like the sinus node. Laser modification of sinus node function could become a form of nonpharmacologic heart rate control in patients with coronary artery disease undergoing surgery and in the syndrome of inappropriate sinus tachycardia. (Circulation 1990;81:350–359)

Pharmacologic control of excessive sinus tachycardia in humans is occasionally limited by side effects inherent to the drugs used, patient intolerance, or treatment failure related to the nature of the disease.1,2 Therapeutic options for severe cases of drug-resistant sinus tachycardia today include total surgical exclusion of the sinus node region or cryosurgical ablation.3,4 Both procedures usually result in atrial or atrioventricular junctional escape rhythms and necessitate implantation of a permanent pacemaker.

The functional anatomy of the sinus node region in humans and dogs is unique in that it shows widespread distribution and rate differentiation of the pacemaker complex with predictable shifts in the sites of impulse origin with changes in the autonomic tone and with certain pharmacologic interventions.5–7 We hypothesized that such a rate differentiation may prove to be advantageous in attempting selective, graded ablation of sinus node areas responsible for fast heart rates only, with preservation of pacemaker sites responsible for normal heart rates. Based on our experimental and clinical experience with surgical treatment of ventricular tachycardia,8–10 neodymium:yttrium-aluminum-garnet (Nd:YAG) laser photocoagulation seemed to be an optimal and simple ablative technique for creating visually controlled, circumscribed, sharply demarcated lesions with preservation of myocardial structural integrity. The purpose of this experimental study was to test...
the feasibility and long-term effects of intraoperative Nd:YAG laser modification of sinus node function.

Methods

Seventeen healthy mongrel dogs of both sexes weighing 21–39 kg were included in the study. All animals underwent the same series of preoperative and postoperative testing described below. Group 1 included 10 animals that received sodium pentobarbital anesthesia. Four animals in group 2 were anesthetized with morphine and α-chloralose. These two anesthetic agents were used to ensure that the activation sequences existed throughout a wide range of heart rates. Three animals in group 3 underwent a sham procedure (mapping but no lasing) under sodium pentobarbital anesthesia. All procedures performed in this study followed the appropriate institutional guidelines and the American Heart Association guidelines for animal research.

Surgical Procedure

Animals in groups 1 and 3 were anesthetized with sodium pentobarbital, 30 mg/kg i.v. Group 2 animals received 1.5 mg/kg morphine sulfate s.c., followed in 15 minutes by an infusion of 100 mg/kg α-chloralose i.v. All animals were ventilated by a Harvard respirator (South Natick, Massachusetts) on room air. A right thoracotomy was performed in the fourth or fifth intercostal space. The heart was suspended in a pericardial cradle. Reference electrodes were sewn on the anterior surface of the right atrium near the right atrial appendage and at a caudal site close to the atrioventricular groove. Mapping was performed with a 5-mm diameter hand-held bipolar probe with an interelectrode distance of 2 mm. The entire anterior surface of the right atrium, adjacent rims of the superior and inferior vena cavae, and adjacent portions of the back of the right atrium at both caval junctions were sequentially mapped. During the mapping studies, two surface electrocardiographic leads (II and III), bipolar electrograms from the two reference electrodes, and one bipolar and two unipolar electrograms from the mapping probe were simultaneously displayed on a multichannel oscilloscope and were recorded by an ink-jet recorder (Siemens Mingograf) at paper speeds of 250 mm/sec during mapping and at 100 mm/sec during the lasing procedure. Band pass filters of 0.15–30 Hz were used for the surface electrocardiograms, 50–1,000-Hz filters were used for the bipolar electrograms, and 0.15–1,000-Hz filters were used for the unipolar electrograms. Local electrical activation was identified as the first sharp component in any of the unipolar electrograms and was measured to one (or both) of the reference electrograms. The mean (+SEM) number of mapped points was 42.2±1.8. Activation timing was reproducible within a spatial resolution of 5 mm, and measurements were accurate to 2 msec. Electrical maps were created from data where major beat-to-beat pacemaker shifts could be excluded with a high degree of certainty. In groups 1 and 3, spontaneous pacemaker shifts were uncommon; in group 2, they were more common. Beat-to-beat shifts in the points of impulse origin ("O points") were not observed in any animal during isoproterenol infusion.

After the site of earliest right atrial activation (O point) was identified, an isoproterenol infusion was begun. The lowest isoproterenol infusion rate resulting in maximum attainable heart rate was used, and the new sinus O point on isoproterenol was determined. Laser photocoagulation was applied to the O point during isoproterenol infusion and stepwise to remapped new O points until 30±5% decrease in heart rate occurred. This end point was chosen arbitrarily. Lasing was performed with a continuous wave Nd:YAG laser (MediLas II, MBB-Medizintechnik) coupled to a 600-μm gas-cooled silica quartz fiber with an irradiating spot size of less than 5 mm. Laser power emitted at the tip of the fiber was set at 30 W. Epicardial lasing of the mapped sinus O point resulted in immediate acceleration of the heart rate followed by deceleration. After deceleration had occurred, the laser beam was directed to a more caudal site. Lasing was suspended after irradiation of two or three adjacent areas to allow for remapping of new O points. After the preset decrease in heart rate had been achieved, lasing was terminated, and detailed mapping was again performed. In group 3 (control animals), a similar procedure was performed without lasing. Anesthesia and the amount of handling of the right atrium was the same in groups 1 and 3. Ten weeks after the initial procedure, 10 of the 17 dogs underwent a second thoracotomy. Electrical mapping of the right atrium was performed before and during isoproterenol infusion, and the hearts were removed for histologic evaluation. Seven animals underwent the second surgical procedure 6 months after the initial laser surgery.

Holter Monitoring

The 24-hour Holter monitoring was performed twice before operation, immediately after the laser procedure for 2 consecutive days, on day 7, and at 2, 6, and 10 weeks. In seven animals kept for longer follow-up, a 6-month Holter study was also performed. Postoperative pain and analgesics used during the first 24 hours might have influenced the day-1 Holter results. By day 7, however, the experimental animals were in no distress, and they did not receive any medication. Intrinsic heart rate was determined by pharmacologic blockade of the autonomic tone. This was performed in the awake dogs by injection of propranolol, 0.5 mg/kg i.v. during a 3-minute period, and 10 minutes later by injection of atropine, 0.2 mg/kg i.v. The Holter tapes were scanned by a Holter analyzer (Marquette Electronics). The 24-hour full disclosures were recorded at 3 mm/sec. Strips of the lowest and highest spontaneous heart rates and intrinsic rates after propranolol and atropine administration were also printed out at 25 mm/sec. The average and maximum heart rates were determined for each
1-hour period and for the full 24 hours. Normal dogs tend to have episodes of marked sinus bradycardia with sinus pauses measuring several seconds. This behavior precluded a meaningful statistical assessment of the changes in minimum heart rates induced by the laser intervention. Heart rate trend curves were constructed throughout each 24-hour period. Of the 51 first week studies, seven were technically unsatisfactory; all other Holter studies were repeated until satisfactory.

**Catheterization Studies**

Electrophysiologic evaluation and isoproterenol testing of the spontaneous pacemakers were performed under general anesthesia before operation, 1, 2, 6, and 10 weeks after operation, and at 6 months. Anesthesia was always the same as during surgery. On each occasion, 12-lead electrocardiograms were recorded at paper speeds of 25 and 100 mm/sec, and leads II and III were continuously monitored. Heart rates were determined from 10 consecutive cycles. An isoproterenol dose-response curve was constructed with an infusion pump delivering 10 different dosages of isoproterenol from 0.125 to 10.0 µg/min. After a wash-out period of 10 minutes, a 6F quadripolar catheter electrode with 6-mm interelectrode distances was introduced with the Seldinger technique through a femoral vein and was advanced under fluoroscopic control to the high right atrium for pacing and recording local bipolar electrograms. Pacemaker recovery times were determined after pacing for 90 seconds at cycle lengths of 400, 350, 300, and 250 msec. Pacemaker recovery times were also determined after autonomic blockade. In group 2 dogs after operation and during morphine-chloralose anesthesia, propranolol induced severe bradycardia, which occasionally necessitated temporary right ventricular pacing.

**Histologic Evaluation**

The hearts were randomly assigned to three histology groups: group A, five hearts; group B, five hearts; and group C, seven hearts. From groups A and B, a block was taken containing the sinoatrial node and its approaches up to the region of the inferior vena cava and serially sectioned. Every 20th section from group A and every 10th section from group B were retained. In group C, the sinoatrial node and its approaches were taken as one block, and a second block was taken at the region of the inferior vena cava. Both blocks were serially sectioned, and every 10th section was retained. All sections were alternately stained with hematoxylin-eosin and Weigert-van Gieson stains. In this manner, a mean of 428 sinoatrial nodal and 437 inferior vena cava sections were examined for each experiment.

**Statistical Methods**

The Student's paired t test was used to compare changes in spontaneous heart rates during Holter monitoring, maximum heart rates during isoproterenol infusion, intrinsic heart rates during autonomic blockade, and pacemaker recovery times. Data were expressed as mean±SEM. Semilogarithmic isoproterenol dose-response relations were calculated with a linear regression analysis. Slopes and intercepts of preoperative and postoperative regressions were compared with analysis of variance (ANOVA). Preoperative and postoperative comparison of pacemaker recovery time to spontaneous pacemaker cycle length relation was performed by ANOVA. In all statistical tests, a significance level of 0.05 was used.

**Results**

**Short-term Effects of Lasing**

During surgery before isoproterenol infusion, electrical O points were localized in various portions of the sulcus terminalis (Figure 1A). In all but one animal, isoproterenol infusion shifted the O point to a localized area at the edge of the anterior and posterior surfaces of the right atrium between the superior vena cava and the base of the right atrial appendage (Figure 1B). Isoproterenol infusion invariably resulted in acceleration of the heart rate and peaking of the P waves in electrocardiographic leads II and III. During laser photocoagulation of the O point, the heart rate accelerated; this was followed by immediate deceleration to a rate slower than that before lasing. With progressive increments in the irradiated surface area, the following changes were observed: 1) the heart rate progressively decelerated; 2) amplitude of the P waves progressively diminished; and 3) new O points were observed at the caudal edge of the lased area. Epicardial lasing was continued until a 30±5% decrease in heart rate occurred. Before lasing, mean heart rate on isoproterenol was 205.0±5.2 beats/min; after lasing, it decreased to 144.9±5.2 beats/min (−29.3%, p<0.05). Lasing always proceeded from the O point in a caudal direction. In four animals, this resulted in stepwise decrease in heart rate with stepwise shift in the O point to the lased margin. In 10 animals, the stepwise deceleration was interrupted by an abrupt decrease in heart rate accompanied by a shift in O point to a location away from the lased margin. Achieving the predetermined decrease in heart rate usually required irradiation of a strip 1 cm wide and about 2.5 cm long. This strip encompassed both sides of the superior vena caval–right atrial junction at the rostral sulcus termini, and about 0.5 cm to the back of the right atrial–superior vena caval junction (Figure 1C). The total lased area in the 14 animals was 2.74±0.24 cm², and the total laser energy delivered was 4,020±549 J (range, 1,780–9,720 J). The lased area was approximately measured by measuring the length and width of the coagulated atrial surface. Immediately after photocoagulation, the new O points during isoproterenol infusion were usually located at various portions along the sulcus terminalis, at some distance from the caudal edge of the lased area (Figure 1D). In two animals, the O point after lasing was located on the caval side of the inferior vena cava–right atrial
junction. In no case did an atrioventricular junctional escape rhythm emerge. In the control animals (group 3), no change was observed in heart rate, P wave configuration, or atrial activation sequence.

Electrocardiographic and Pharmacologic Follow-up

P wave configuration. In all group 1 animals, 12-lead electrocardiograms on the follow-up examinations showed normal heart rates and normal P wave axes in the frontal and horizontal planes. During morphine-chloralose anesthesia (group 2), the heart rates were slow, and ectopic or multiform P waves and occasionally atrioventricular junctional or ventricular escape rhythms were observed.

Holter monitoring. Results of the ambulatory electrocardiographic monitoring in all animals undergoing laser photocoagulation (groups 1 and 2 combined) are summarized in Figure 2. The average...
24-hour heart rates decreased by 17.4±5.0% at 10 weeks (p<0.01) and by only 8.6±7.2% at 6 months (NS). The maximum heart rates on Holter, however, decreased by 30.5±3.5% at 10 weeks (p<0.001) and by 33.8±1.7% at 6 months (p<0.001). The “intrinsic” heart rates decreased by 32.7±3.5% at 10 weeks and by 18.5±4.2% at 6 months. As seen in Figure 2, most of the changes occurred between the preoperative and 1-week postoperative Holter testing; thereafter, no further significant changes were observed. The 24-hour heart rate trend curves constructed from the Holter recordings showed characteristic changes. Before the laser procedure, the full range of heart rates occurred several times during the day. After laser photoablation of the sinus node, however, the top portions of the heart rate trend curves were conspicuously clipped off. A representative example is illustrated in Figure 3. Similar changes were not observed in the control group.

Isoproterenol dose-response curves. Isoproterenol dose-response curves displayed an interesting pattern. Because the effects of isoproterenol were tested under two types of general anesthesia, these dose-response curves were analyzed separately in the three groups of animals. In group 1, at relatively low doses of isoproterenol the slopes of the preoperative and postoperative curves ran a fairly similar course (Figure 4). At higher doses of isoproterenol, however, the maximum postoperative heart rates were “capped off” (Figure 4). These changes persisted up to 6 months. In individual cases, maximum heart rates on Holter were similar to maximum rates during isoproterenol infusion. In group 2, isoproterenol dose-response curves had a different shape with heart rates increasing more gradually with increasing isoproterenol doses. Each postoperative dose-response curve was depressed in this group compared with the preoperative curve (Figure 5). In group 3 (control animals), the isopro-
terenol dose-response curves remained unchanged (Figure 6). Mathematical analysis was performed with the ANOVA test comparing heart rate with the log₁₀ of the isoproterenol dosage. In group 1, the slopes and intercepts were significantly different at 10 weeks compared with the preoperative values (F=22.7; df=1, 16; and F=218; df=1, 17, respectively). In group 2, similarly significant changes were found in the slopes and intercepts (F=7.44; df=1, 16; and F=130; df=1, 17, respectively).

Electrophysiologic Evaluation

In group 1, maximum pacemaker recovery times at 10 weeks were 25.2±2.5% longer compared with the maximum preoperative pacemaker recovery times (p<0.05). In group 2, a similar comparison could not be performed because of sporadically long recovery times terminated by atrioventricular junctional escape beats. In the control group (group 3), recovery times decreased by 4.3±9.4% (NS). The recovery times after autonomic blockade behaved in a similar fashion: in group 1, pacemaker recovery times increased by 30.5% at 10 weeks; in group 3, there was no significant change.

To further characterize the behavior of the pacemaker after partial laser photocoagulation of the sinus node, preoperative and postoperative recovery times were compared with the spontaneous pacemaker cycle lengths. The relation between recovery time and cycle length was nearly identical and linear,
Morphological Studies

At the 10-week and 6-month reoperations, the lased areas were replaced by cartilage formation from moderate-to-severe degree in all cases with occasional bone formation (Figure 7, left). In addition, there was fibrosis and chronic inflammatory cells. The sinoatrial node was not identified in lased cases. There was considerable pericarditis in all. Some of the atrial cells closer to the region of the tail end (caudal or most distal cells from the sinoatrial node toward the inferior vena cava) were large and pale and bore some resemblance to Purkinje cells (Figure 7, right).

Discussion

This study suggests that selective Nd:YAG laser photocoagulation of sinus node regions showing earliest activation during catecholamine stimulation can effectively abolish excessively fast heart rates while preserving an acceptable overall pacemaker rate responsiveness.

The theoretical basis of partial sinus node ablation is well founded. Early in this century, Lewis et al.\textsuperscript{13} performed a series of experiments evaluating the site of origin of the canine heart beat. They found that the sino-auricular node is placed beneath the sulcus terminalis and usually extends from the angle formed by the superior vena cava and free margin of the appendix along the sulcus to the angle of junction of superior and inferior vena cava. The chief mass of tissue is usually placed in the neighbourhood of the cavo-auricular angle where it lies just beneath the surface of the epicardium. Its termination is not clearly defined, but tapers away. As it is traced in the direction of the inferior vena cava, it diminishes in size until it thins out into a fine and often broken thread, the end of which is more deeply placed and approaches the endocardium.\textsuperscript{13} They found spontaneous and vagally induced “migration of the seat of impulse formation from the head to the tail of the S-A node.”\textsuperscript{13,14} With vagus stimulation they occasionally found a shift of the origin of the impulse to the vicinity of the inferior vena cava along the sulcus terminalis. Similar pacemaker shifts have been reported by Meek and Eyster.\textsuperscript{15} Later, pacemaker migrations along the sulcus terminalis were observed by several investigators using either in situ mapping or microelectrode studies combined with vagal\textsuperscript{16} or sympathetic nerve stimulation,\textsuperscript{17-19} administration of norepinephrine\textsuperscript{17,18} or isoproterenol.\textsuperscript{20} Also, shifts in pacemaker sites within the sinus node may influence the time course of atrial excitation. These shifts can result in changes in the P wave configuration.\textsuperscript{20,21} From 1978 to 1980 Boineau et al.\textsuperscript{5,6} and Schuessler et al.\textsuperscript{22} advanced the concept of “the pacemaker complex.” Using a computerized mapping system, they showed separate origin points dominating...
excitation within specific ranges of heart rates.\textsuperscript{5,6,22} They have also found that spatial distribution of the “pacemaker complex” exceeded the dimensions of the histologically defined canine sinus node by a factor of 3–4.\textsuperscript{6} More recently, the same investigators have also shown a widely distributed atrial pacemaker complex in the human heart.\textsuperscript{7}

Several techniques including surgical excision,\textsuperscript{23–28} cauterization,\textsuperscript{6,29} and incision and suture\textsuperscript{6} have been used to study the effects of partial or total elimination of sinus nodal tissues. These procedures often resulted in early appearance of coronary sinus or atrioventricular junctional rhythms that were later replaced by atrial escape rhythms.\textsuperscript{23,24,26,28,30,31} Jones et al\textsuperscript{32} performed stepwise excisions of right atrial tissue segments beginning at the sinoatrial node and extending caudally along the sulcus terminalis to the junction of the inferior vena cava and inferior right atrium. In the acute open-chest canine preparation they found atrial, atrioventricular, and ventricular ectopic pacemakers to emerge. Each successively inferior focus had a slower rate than the sinus node itself. Follow-up of the subsidiary pacemaker function was not performed in these experiments.\textsuperscript{32}

Based on these previous investigations, we chose a technique of selective sinus node ablation that held promise for therapeutic rate differentiation and clinical applicability. The combination of laser photocoagulation, isoproterenol infusion, and repeated remapping of the pacemaker O point proved to be useful in graded elimination of fast heart rates that could be interrupted at any preset value. With this approach, the animals recovered uneventfully and led a normal life during follow-up for up to 6 months. Postoperative electropharmacologic studies and ambulatory monitoring revealed a stable pacemaker and a normal average heart rate without episodes of physiologically or pharmacologically induced tachycardia. Severe postoperative bradycardia only occurred in a few animals as a result of morphine-chloralose anesthesia combined with high doses of propranolol, a clearly nonphysiologic situation. Severe bradycardic episodes were not observed in the nonanesthetized animals during Holter monitoring, even when large doses of propranolol were administered. Spontaneous episodes of very fast heart rates on the other hand have been totally eliminated, and heart rates during isoproterenol infusion could not reach pre-

**Figure 7.** Left: Photomicrograph of the sinoatrial nodal area showing the sinoatrial node replaced by cartilage, bone, and fibrosis. Weigert-van Gieson stain; original magnification, \( \times 17.2 \). B, bone; C, cartilage; F, fibrosis. Arrows point to the caudal end of the lased area where some of the atrial cells are large and pale looking. Right: Higher power of the large, pale-looking cells at the caudal edge of the lased area. Weigert-van Gieson stain; original magnification, \( \times 180 \). A, atrial muscle. Arrows point to the large, pale cells.
operative levels. Intrinsic heart rates have also decreased. Our dogs were not trained for treadmill, and the effects of graded exercise on subsidiary pacemaker function were not tested.

The results of this study helped to gain insight to certain physiologic problems regarding sinoatrial structure and function in the dog. Of interest, despite the ability to deliver precisely dosed laser energies to precisely defined areas, a considerable amount of atrial tissue had to be photocautagulated before a significant decrease in heart rate occurred. The critical areas of right atrium always included the rostral end of the sulcus terminalis and the adjacent rim of the superior vena cava. In addition, they usually involved a narrow edge at the back of the proximal right atrium. In several dogs, photocautagulation of the caval side of the proximal sulcus terminalis was critical for achieving the preset decrease in heart rate. Experiments were not performed where a similar area would have been lased in a blind fashion, without electrical activation mapping. Therefore, it remained uncertain whether the mass of sinus node area ablated or the actual site of pacemaker activity was more critical to the successful results. Immediately after lasing, the pacemaker shifted to various areas along the distal sulcus terminalis and occasionally even to the inferior caval surface (Figure 1D). At 10 weeks and 6 months, the remapped O points were shifted slightly toward the vicinity of the edge of the lased area suggesting an origin from the caudal sinoatrial node. This differed from the findings of Rozanski et al. Under different experimental conditions, they found that atrial pacemakers emerging soon after removal of the sinoatrial node were the same that ultimately controlled the heart.

The increase in pacemaker cycle lengths and recovery times in our experiments were similar to those observed by Randall et al after surgical excision of the sinus node. In our experiments, however, several pieces of indirect evidence suggested that the sinus node had not been totally eliminated. First, postoperative mapping has shown that subsidiary pacemakers were located in the immediate vicinity of the lased area at anatomic sites that had been shown by previous histologic and electrophysiologic studies to incorporate the tail of the sinus node. Second, the electrophysiologic characteristics of the subsidiary pacemakers at the 10-week restudy displayed remarkable resemblance to those of the preoperative sinus pacemakers. Although the spontaneous cycle lengths and recovery times were significantly longer after the laser treatment, the recovery time and spontaneous cycle length relation remained practically unchanged, which suggests similar preoperative and late postoperative pacemaker characteristics. Third, P wave axis remained normal. Finally, histologic studies performed at 10 weeks and 6 months occasionally revealed the presence of pacemaker-like cells resembling sinus node cells in the vicinity of the lased area.

The clinical applicability of intraoperative epicardial laser irradiation of the sinus node area has yet to be determined. Inappropriate sinus tachycardia, a rare condition, is quite refractory to currently available medications, and other forms of atrial tachyarrhythmias could also benefit from a similar laser procedure. Irradiation of the sinus node during coronary artery bypass grafting may be potentially useful in selected patients for long-term control of heart rate response after operation to reduce ischemia by reducing myocardial oxygen demands.

In summary, this study shows that 1) map-guided graded laser photocautagulation of sinus node regions having earliest activation during catecholamine stimulation successfully limits maximum heart rates without causing significant bradycardia; 2) the effects are long lasting; and 3) the remaining pacemaker behaves like the sinus node. The clinical applicability for nonpharmacological heart rate control merits exploration.

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References


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