ORIGINAL ARTICLE

Growing Pains: Are They Due to Increased Growth During Recumbency as Documented in a Lamb Model?

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Abstract: The rate and patterns of longitudinal bone growth are affected by many different local and systemic factors; however, uncompromised growth is usually considered to be smoothly continuous, with predictable accelerations and decelerations over periods of months to years. The authors used implanted microtransducers to document bone growth in immature lambs. Bone length measurements were sampled every 167 seconds for 21 to 25 days. The authors show that at least 90% of bone elongation occurs during recumbency and almost no growth occurs during standing or locomotion. The authors hypothesize that growth may also occur in children during rest or sleep, thus supporting the concept of nocturnal growth and perhaps a relationship to growing pains.

Key Words: growing, pains, growth, physis

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Our perception for growth in children is influenced by the Centers for Disease Control and Prevention (CDC)'s human growth curves. Children's heights are measured annually, semiannually, or rarely quarterly, and the raw data are then smoothed mathematically, creating mean continuous growth curves and paralleling percentile curves.[8] One could infer that a similar continuous growth pattern occurs over shorter time periods such as weekly or even daily. Interestingly, Lampl et al, instead of measuring the heights of children yearly, measured the heights of children daily and presented the growth pattern of each child as an individual. From these studies a different pattern of human growth emerged, described as growth by saltations and stasis.[9,10] Within a brief 1- to 3-day interval, children grew 1 cm or more, and this was followed by a much longer period of 10 to 50 days when no demonstrable growth occurred. This pattern has been detected in children at all ages from infancy to adolescence. In this saltations and stasis pattern, the lengths of both the static and saltatory periods are arrhythmic, and the height of the saltation is unpredictable.

For years, parents and pediatricians have empirically noted differences in growth rates in their children and patients, which result in spurts of height. Some have hypothesized that children grow more at night than during the day, yet few data exist to corroborate these impressions. In addition, many children will present to their family provider for evaluation of nocturnal lower leg pain. Typically a child will awaken in the middle of the night with poorly defined pain in the legs for which relief is often gained from rubbing the legs, heat packs, or various medicines such as acetaminophen or nonsteroidal anti-inflammatories. Evaluation of this constellation of symptoms with laboratory and radiologic studies is often fruitless, and families and practitioners are resigned to consider a diagnosis of "growing pains,"[2] a diagnosis of exclusion that is based on two unproven tenets: that children grow more at night, and that it is this cyclic growth that results in the pain and discomfort.

In this study, we used implanted microtransducers to document growth in an immature lamb model. With this technology, we could record growth on a nearly instantaneous basis with exceedingly fine spatial and temporal resolution. We hypothesized that growth is not smoothly continuous, and we endeavored to demonstrate behavioral activities that may affect the growth rates.

MATERIALS AND METHODS

We chose to measure the pattern of bone elongation in lambs for two reasons. First, their relatively large size makes the microtransducer virtually transparent. Second, in comparison with other experimental mammals, lambs have a long growth period, not reaching adult height until about 1 year of age and with growth plates that remain open until about 4 years of age. Before performing this study, approval was obtained from the University of Wisconsin Institutional Animal Care and Use Committee.

Three sets of twin male lambs were acquired as weanlings and handled daily to acclimate them to their physical environment, including the presence of people. At 8 to

Study conducted at the School of Veterinary Medicine, University of Wisconsin, Madison, Wisconsin.

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12 weeks of age, under surgical anesthesia, two microtransducers were implanted in one randomly chosen tibia of one lamb.[22] One microtransducer spanned the proximal tibial growth plate and recorded the pattern of bone elongation. A second (control) microtransducer spanned a central nonelongating diaphyseal region. Placement of the devices was verified using intraoperative fluoroscopy and reconfirmed at necropsy. The lambs received analgesics for 24 hours following implantation surgery, after which, by multiple clinical criteria, they appeared to be without pain and were freely ambulatory.

Stabilizing the microtransducers to the tibia, we used a double screw technique, a screw within a screw (Fig. 1). First, after drilling and tapping the epiphyseal and metaphyseal screw holes, we inserted a fully threaded 3.5-mm cannulated cortical bone screw. Subsequently, a screw specially designed and fitted for the modular clamps of the microtransducer was cemented with polymethylmethacrylate inside the lumen of the cannulated bone screw. A uniquely designed siliconized sleeve protected against fibrosis while not inhibiting micromovements of the device. At the termination of the experiments, the microtransducers/transmitters (calibrated before implantation) were recovered and recalibrated and were found to be between 0.2% and 5% of their starting points.

The twin lamb was kept in an adjacent pen, which furthered socialization. Daily growth, behavioral data, and force plate data acquired 2 weeks into the experimental period were collected from both the experimental lamb and the twin as a confirmation of normal activity under these environmental conditions.

These microtransducers have a spatial resolution of 5 μm, and, by telemetry, measured changes in tibial bone length in unrestrained lambs every 167 seconds over a 3- to 4-week period. The exact form of the data stream was nine replicates of each transducer position; the replicates were extremely consistent, with the standard deviations of the replicates averaging 1 to 3 μm. The lambs were monitored constantly with a video camera synchronized with the recordings from the telemetry system. A digital image of the lambs was captured each minute of the study. From these images we characterized the activities of each lamb as either lying down ("recumbent") or walking or standing ("standing").

At the end of each study, the lamb was killed and the total displacement was verified by direct measurement of the distances between epiphyseal and metaphyseal screws and by measuring the distances on anteroposterior radiographs. In addition, oxytetracycline (OTC) pulse labeling provided rate-of-elongation data on the final day of the study. This was performed by giving an OTC injection 2 days before euthanasia and an alizarin complexone injection 1 day before euthanasia. The distance between the fluorescent markers, the distance of growth over 24 hours, was used as verification of the growth as recorded by the microtransducers.

A morphologic and stereologic analysis was done of the proximal tibial growth plate of the implanted limb and the control limb to determine whether implantation of the microtransducers had any effects at the cellular level. Growth plate cartilage was fixed in the presence of 0.7% ruthenium hexamine trichloride and embedded in plastic. Section 1.5 μm thick were cut, mounted, stained with methylene blue/azure II/basic fuchsin on plastic-embedded sections, and measured stereologically from both the operated and nonoperated limbs. We recorded cellular indices (cell density, cell volumes) within the proliferative and hypertrophic zones.[20]

RESULTS

While we report on the results of three lambs, we actually implanted microtransducers in three additional lambs, six lambs overall. In early studies we experienced premature failures at the cable–device interface, and we experienced one incident of premature battery failure. Subsequently, with substantial improvements in the cables and the battery, we extended the potential life of these devices and recorded data for 21 to 25 days.

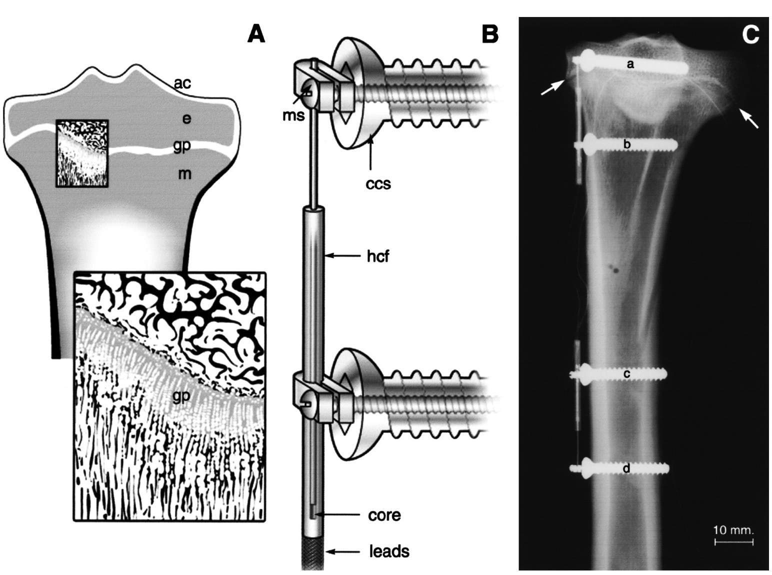

FIGURE 1. A, Example of a growing tibia. In this experimental method, one cannulated screw is placed in the epiphysis (e) and the second screw is placed in the metaphysis (m). B, The microtransducer is cemented into the cannulated screws, which have been placed as described above. C, At necropsy, a radiograph demonstrates the surgical set-up with a microtransducer spanning the growth plate. The control microtransducer is placed at the mid-tibial diaphysis.

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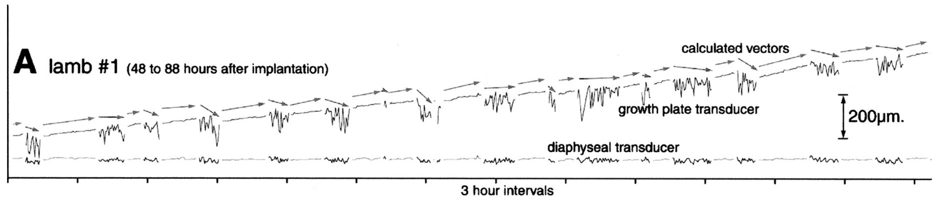
FIGURE 2. A representative growth curve from lamb 1. The lower, diaphyseal tracing reveals no increase in length. The upper, growth plate transducer tracing demonstrates gradual displacement consistent with growth. High-frequency signal with a negative slope alternated with low-frequency signal and a positive slope.



From the microtransducers, we noted that the patterns of bone elongation at the proximal tibial physis and the diaphyseal microtransducer (control) were similar in each of the three lambs (Fig. 2). Data from the growth plate transducer (simple linear regression of all data points) showed a positive slope consistent with an average rate of elongation of the proximal tibia of 231, 284, and 248 μm/day for the three lambs, respectively (Table 1). Data from the diaphyseal transducers (simple linear regression of all data points) were consistent with a slope equal to zero (ie, no elongation over the study period).

At a finer scale, the signal pattern of elongation from the growth plate transducer was clearly nonlinear and consisted of a bimodal alternating pattern of a period with a high positive slope that exceeded the slope of overall elongation followed by a period of a relatively high-amplitude signal with a net negative slope (Fig. 3). Concurrent digitized images of the lambs confirmed that in every case (every lamb, interval, day, in each study), the high positive slope occurred while the lamb was recumbent, while high-amplitude negative slope occurred while the lamb was standing, walking, or running. In every case, the transition from high positive slope to high-amplitude negative slope was a transition from recumbency to standing, while the opposite signal transition was a transition from standing to recumbency. At the same time, the diaphyseal sensor also was recording a synchronous bimodal pattern; however, both during recumbency and during standing or ambulation, the slopes of the data were zero (no elongation).

To quantify the amount of growth that occurred during recumbency versus standing, we converted all the data from each recumbency or standing interval to a vector (linear regression of all data for that interval). Each vector had a slope whose components yield time and elongation. Subsequently, mean vectors for each recumbent and standing intervals were calculated for each lamb. Because individual lambs varied significantly in their activity levels, data from each lamb are presented individually.

The number of recumbent periods was 24, 46, and 27 per day, respectively. These periods averaged 41, 20, and 35 minutes, longer than the average standing intervals of 28, 12, and 15 minutes. The mean slope of the vectors for the recumbent periods (649, 561, and 636 μm/d) were significantly higher than the mean slopes for the standing intervals (−444, −562, and −018, respectively) and were essentially double the overall slopes for the entire study (231, 284, and 248 μm/d, respectively). Summing the individual incremental growths for each recumbent period and comparing this sum with total growth for the length of the study leads to the conclusion that in these three lambs, 93.8%, 88.3%, and 89.2% of all growth occurred during recumbency.

Growth during recumbence also is supported by the fact that the average vectors for the standing intervals were all negative. A conclusion from these data (rejecting the nonsensical conclusion that the lamb was shrinking) is that no growth occurred during standing. These negative slopes we interpret as overall biomechanical compression of the growth plate cartilage during loading, and the variability of negative slopes during standing represent the general activity levels of the lambs.

There were no significant qualitative differences between the experimental and control growth plates on histologic evaluation (Fig. 4). Stereologic comparisons between implanted growth plates and control growth plates from the contralateral limb at a range of parameters are presented in Table 2. It appears that no significant differences in morphometric parameters were present at the cellular level. At

TABLE 1. Cumulative Bone Elongation During Standing/Ambulatory and During Recumbency

			Standing/Ambulatory Periods			Recumbency Period		
Lamb	Age (wks)	Overall Rate of Elongation (μm/d)	Ave. Rate of Elongation (μm/d)	Ave. Time Interval Standing (min)	Ave. Number Standing Intervals (per day)	Ave. Rate of Elongation (μm/d)	Ave. Time Interval Recumbency (min)	Growth During Recumbency (% of total growth)
1	12	231	−444 ± 390*	28 ± 3.2	22.69 ± 1.5	649 ± 103*	41 ± 1.6	93.8%
2	10	284	−562 ± 540*	12 ± 0.6	45.79 ± 1.9	561 ± 122*	20 ± 1.0	88.3%
3	8	248	−018 ± 170*	15 ± 1.2	30.49 ± 2.2	636 ± 165*	35 ± 1.9	89.2%

*$P < 0.01$.
Data are given as ± SE.

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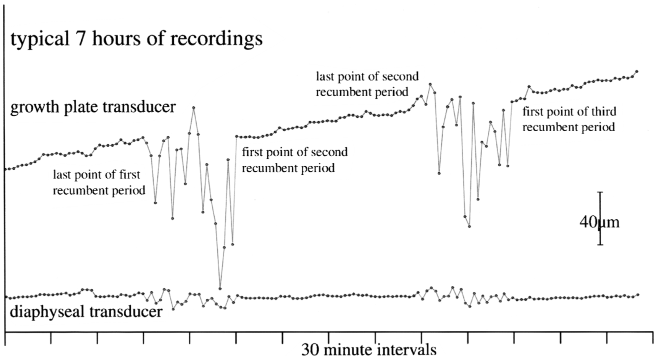

FIGURE 3. Magnification of a typical growth pattern demonstrates alternating low-amplitude signal, which has a positive slope. Calculation of the higher-amplitude signal with linear regression results in a negative slope. The onset of the higher-amplitude signal correlated with standing onset, and the end of the higher-amplitude signal was associated with transition to recumbency.

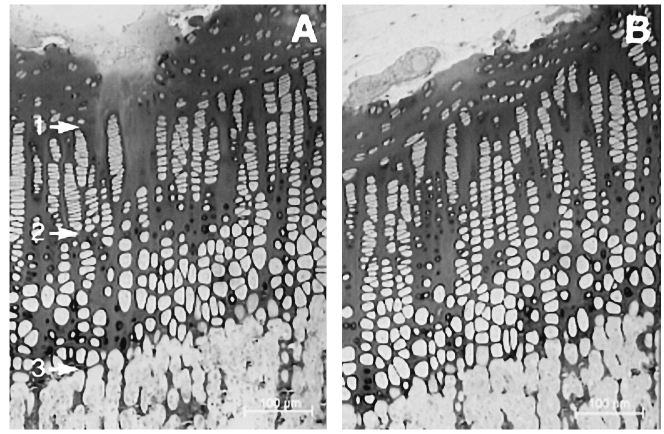

FIGURE 4. Images of sections of plastic-embedded growth plates in the experimental growth plate (A) and the control growth plate (B). No qualitative differences are noted here. Scale bar equals 100 μm.

necropsy, the average rate of elongation was measured by OTC labeling (see Table 2). In this evaluation, we noted a 4.5% increase in growth rate (P = 0.07) on the experimental side (254 μm/d) in comparison to the control tibia (243 μm/d). The small difference between the implanted and nonimplanted tibia is not surprising: the reaction of bone and cartilage to a wide range of stimuli is well known and has been named the regional acceleratory phenomenon (RAP).[5,14]

DISCUSSION

In assessing human growth, we rely upon normative data that are averaged for a group of children who are measured once or twice a year. These data generate well-recognized growth curves, which imply a smoothly continuous increase in height. In this study, we used implanted microtransducers that record growth on a nearly instantaneous basis in the lamb model. This is the first technology that we are aware of that can quantitate growth rate measured frequently over a period of time. The OTC technique of one rate-of-elongation measurement during the life of the animal had been the finest resolution that was available before this study. Simply put, the current implantable technology allowed us to apply a magnifying glass to the growth curve of lambs, and at least in this model, we noted that growth is not smoothly continuous.

In the lamb, we found that overall growth consists of a period of rapid elongation with low-amplitude fluctuations. This pattern alternates with high-frequency fluctuations with no or negative growth as measured by microtransducers. The oscillations recorded by both transducers are thought to represent strains at the growth plate and in diaphyseal bone. We interpret these larger oscillations as growth plate compression (negative direction) and elastic recoil and/or growth plate tension (positive direction). Similarly, the oscillations in the diaphyseal transducer signal, while much smaller, are synchronous with oscillations from the growth plate transducer.

When correlated with the activities of the lambs, it is clear that the low-amplitude periods with rapid increase in growth occur during recumbency. The high-amplitude, negative growth slope is associated with activities such as walking or standing. We interpret these negative slopes as overall

TABLE 2. Comparisons of Implanted Growth Plate With Control Growth Plate From the Contralateral Limb

	Implanted	Control
OTC labeling		
Rate of elongation (μm/day)	254 ± 13*	243 ± 13*
Growth plate height (μm)	478 ± 56	488 ± 39
Histomorphometric analysis		
Volume fraction proliferative cells	0.21 ± 0.02	0.22 ± 0.02
Volume proliferative cells (μm^3)	1,590 ± 290	1,550 ± 250
Density proliferative cells (cells/mm^3)	136,900 ± 24,600	142,200 ± 24,100
Volume fraction hypertrophic cells	0.46 ± 0.04	0.46 ± 0.04
Volume hypertrophic cells (μm^3)	9,530 ± 1,730	9,410 ± 1,360
Density hypertrophic cells (cells/mm^3)	49,500 ± 6,620	49,200 ± 6,920
Chondrocytes turned over/day	9,360 ± 1,300	8,620 ± 1,200

*P = 0.07

biomechanical compression of the growth plate cartilage during loading. The variability of negative slopes during standing represent the general activity levels of the lambs. It is important to note that lambs were not simply standing, and therefore not just statically loading the growth plate. Whether they were loading the limb during a stance phase or whether a limb were unloaded during a swing phase at the moment (once every 3 minutes) of data collection was unknown.

From these data, we observe that 90% of growth occurred during recumbency. Because of slight asynchronies between data collection and video image capturing of the lamb (once per minute), there was some imprecision and uncertainty as to whether some data at the transition from or to standing belonged to the standing interval or the recumbency interval. While we assign about 90% of growth to recumbency, the remaining growth is assigned to this transitional period, and we are uncertain whether it occurred during recumbency or during standing. In this study the lamb's behavior was not manipulated and was similar to the behavior of the control twin in an adjoining pen. Why a lamb would choose to stand or lie down is mostly unknown, and aside from speculation, we have very few data to answer the question, "What would happen if a lamb stood for an extended period of time?"

It is critical to understand whether the implantation of a microtransducer across the growth plate alters the normal pattern of growth. At present there is no independent way to detect a bone-elongation pattern on either an instantaneous or continuous basis during this kind of experiment; however, we also used multiple measurements of growth plate function. From histologic study we demonstrated that there was no significant difference in cellular organization and no distortion compared with the contralateral control tibia. Multiple comparisons (whole animal level) between the lamb with the transducer and his twin showed no differences in weight gain, force plate analysis, and number of recumbent periods per day. In addition, multiple measures of growth plate function at both the organ (OTC labeling) and cellular level (histomorphometry) failed to reveal differences with the control tibia, indicating that implantation of microtransducers has a minimal effect on the normal biology of bone elongation in the instrumented tibia.

In this study we did not endeavor to determine why standing and activity had a compressive effect on growth and why recumbency seemed to stimulate growth. Several mechanisms may exist, including increased growth at rest due to elevations in growth hormone (GH) and insulin growth factor (IGF-1). Our results are consistent with what is known about GH secretion rates and sleep in lambs. In lambs, the highest GH instantaneous secretion rates occur during all resting periods, including REM sleep, absence of food, and simple recumbency. Perhaps this may be a time when growth plate chondrocytes respond to GH/IGF-1 by cell proliferation.[12]

Alternatively, the results from this study may suggest a method of mechanical signal transduction by which regulatory systems of growth plate chondrocytes are integrated. For instance, the Indian hedgehog (Ihh)/parathyroid-related hormone (PTHrP) inhibitory feedback loop represents a key regulatory point between the end of proliferation and the onset of hypertrophy.[7,11,19] More recently, Wu et al demonstrated that Ihh is inducible through mechanical stimulation.[21] Thus, when growth plate chondrocytes are stimulated by mechanical strain, the inhibitory loop may prevent bone elongation.[13] It is possible that recumbency leads to decreased strain in the growth plate, with subsequent decreased synthesis of Ihh. Therefore, the Ihh-PTHrP inhibitory pathway is turned off and a cohort of growth plate chondrocytes would proceed to terminal differentiation characterized by hypertrophy, the phase during which most bone growth occurs.[3,16,20]

"Growing pains" is a clinical diagnosis made in actively growing children (usually 4–12 years of age),[4] characterized by periodic aching or pain in the lower extremity. Patients complain of deep pain that occurs late in the evening or that wakes them from sleep. The pain is usually bilateral and centered over the legs and thighs; it generally responds well to manual stretching, gentle massage, or oral pain medications such as acetaminophen or nonsteroidal anti-inflammatory medications.[18] The pain does not usually occur in the upper extremities and is not present in skeletally mature adolescents. Because it seems restricted to growing children, Naish and Apley in 1951 adopted the term "growing pains syndrome."[15]

Growing pains usually occur several nights in a row and may resolve only to recur several weeks to months later. Pain is not present in the day and does not limit activities. When faced with this clinical scenario, pediatricians and family practitioners must determine whether these symptoms are classic for growing pains or whether the symptoms are atypical and therefore represent a harbinger of another diagnosis. In these cases, laboratory and radiographic studies are used to rule out more malignant or infectious processes. In children afflicted with growing pain syndrome, the results of the physical examination and such diagnostic tests are normal.[1]

Growing pains are not uncommon; the reported prevalence varies from 4.2%[15] to 13% (boys) or 18% (girls),[17] to as high as 34%.[6] The etiology of growing pains is not known. Several theories exist: an organic pain syndrome that may be found in adults (eg, fibromyalgia) but is not well characterized in children; muscle fatigue after a particularly active day that becomes apparent only at night or at rest in highly active children; or a result of increased growth occurring at night. Unfortunately, the latter scenario is difficult to confirm, as it is reasoned that children grow continuously in the upper and lower extremities; and few data exist to demonstrate that children grow more at night than in the daytime. As such, why would a given child have pain-free daytime prevalenceintervals alternating with painful periods only at night and only in the lower extremities?

In this manuscript we report an interesting phenomenon of increased growth with recumbency in the lamb model. This study was not designed to understand the mechanism and regulation of this pattern. We have not elucidated whether this is a result of some mechanical signal transduction pathway or simply a recoil phenomenon of the growth plate to increase in height once mechanical compression is lifted. If a similar phenomenon exists in children, these data would suggest that in the lower extremity, growth is retarded with activity only to be released with rest and recumbency. At the very least, this information does demonstrate that in ambulatory animals, growth is restricted with standing and ambulation. Perhaps increased growth at night in children is also possible. Is it

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possible that this increased growth at night in weight-bearing extremities may be the origin of growing pains, which tend to occur at this time and in these bones?

Clearly these data cannot begin to suggest that if nocturnal growth is present in children, it may be the cause of growing pains. Yet when this information is combined with Lampl's observation of episodic growth,[9,10] it is not too discordant to hypothesize that the pain seen with growing would occur only at night over short periods, followed by asymptomatic periods. A possible mechanism of pain may result from increased tension in the periosteum as the growth plates spring back from released compression or by some signal transduction mechanism during recumbency.

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