The Relationship Between Basic Multicellular Unit Activation and Origination in Cancellous Bone

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Activation frequency is often used as a measure of basic multicellular unit (BMU) activity in cancellous bone. However, activation frequency expresses the rate of BMU appearance in a histologic slide and not the rate of origination, which is a more physiologic indicator of remodeling activity and is necessary for the development of BMU-level bone remodeling simulations. Using identical assumptions to those for calculating the activation frequency, it is shown that the origination frequency in cancellous bone is equal to the activation frequency divided by the total distance traveled by the BMU and its width. (Bone 25:585–587; 1999)

Key Words: Remodeling, Basic multicellular unit (BMU); Activation frequency; Cancellous bone; Histomorphometry.

Introduction

Bone remodels in a process by which osteoclasts and osteoblasts in basic multicellular units (BMUs) resorb and form quanta of bone over a period of time. This process has been well described in cortical[3] and cancellous[1,2] bone. In either case, the activity of a single BMU can be viewed from two different perspectives. The more common, histomorphometric perspective is the two-dimensional one obtained when a histologic section captures a cross section of a BMU as it travels through the bone tissue. This may also be characterized as the limited view of a local observer who glimpses a snapshot of either resorption or formation as the team of cells passes. The broader, three-dimensional perspective is that of a hypothetical, more remote observer who somehow is able to see the cells of a BMU collect at a site of origination and then progress through the tissue (**Figure 1**), excavating and replacing the calcified matrix until, for whatever reason, they die and the BMU ceases to exist. The latter perspective is more comprehensive, but it cannot be visualized with current technology. It must be imagined and quantified using histologic sections.

There are three key variables used to describe a population of BMUs *in a given volume of bone tissue*: the total number of BMUs; their birthrate; and their mean lifespan. However, as shown in **Table 1**, the conceptualization of these three variables

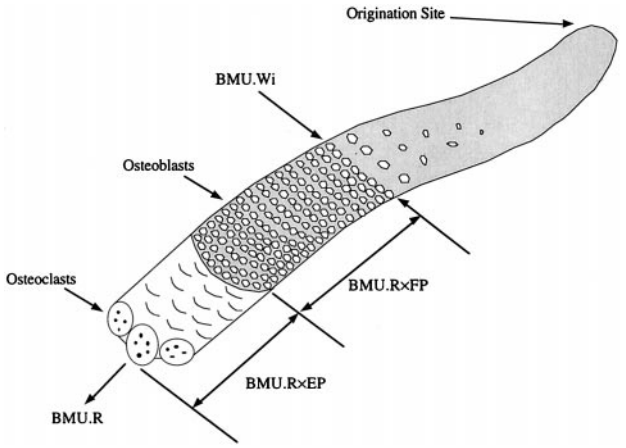

Figure 1. Symbolic view of progressing BMU trench in cancellous bone. The width of the BMU is given by BMU.Wi, and its rate of progression by BMU.R.

in the two-dimensional (2D) and three-dimensional (3D) observational systems has been quite different. For example, the lifespan of a BMU in 2D is equal to the time required for the advancing BMU's resorption and formation activity to pass through a particular plane in the bone, but the 3D lifespan is the total time that these cells travel through the bone tissue as a BMU. The 3D lifespan, called sigma, or σ, in the histomorphometric lexicon, may be considerably longer than the 2D lifespan, called the remodeling period or Rm.P.[6,9] Similarly, the number of BMUs working in a volume of bone tissue is fundamentally different from the number of resorbing and forming sites appearing on a representative section through this volume.

However, the distinction between the 2D and 3D versions of BMU birthrate may be the most important of all. This topic has been discussed previously and is based on assumptions that trabecular osteons are similarly organized to cortical osteons.[7] The 3D version of this variable is the rate at which new BMUs are generated on internal bone surfaces; thus, the units of this variable would be BMUs created per square millimeter of surface per day. This has been referred to as the BMU *origination frequency*,[8,10] and compared to the 2D measure of the birth rate, which has been defined differently in cortical and cancellous bone. In the former, the boundaries of individual BMUs are apparent, allowing their enumeration, and birthrate is defined in terms of the rate at which new BMUs break the plane of the

Table 1. Definitions of three fundamental measures of cancellous basic multicellular unit (BMU) remodeling activity

Variable	View or observation system	
	2D histomorphometry	3D comprehensive view
BMU birthrate	Rate of first penetration of the section plane by passing BMUs	Rate of origination of new BMUs on internal bone surfaces
Lifespan	Time required for the BMU to move through the plane of an imaginary section, from first penetration by osteoclasts to final refilling by osteoblasts	The time that the average BMU exists in the bone, from its origination until all its cells die and its moving resorption-formation activity ceases
Population	The number of BMUs in a particular phase of activity within a section, usually the number of refilling BMUs	The number of active BMUs in a volume of bone tissue

section. This variable is expressed in units of BMUs per square millimeter of tissue per day. In cancellous bone, where the boundaries of individual BMUs cannot be ascertained, activation frequency is usually defined in terms of the rate at which BMUs act on a representative trabecular surface. Here the units are 1/days.

One drawback with the 2D definition is that the activation frequency is not expressed in reference to the amount of bone surface. Because all remodeling occurs on bone surfaces, knowing the number of BMUs per unit surface of bone allows accurate comparison between samples with different surface sizes and is very useful for quantifying bone remodeling. Another difficulty with the 2D measure is that it will be found to be the same in a situation where one BMU is created and progresses a distance R as when three BMUs are created and progress a distance $R/3$, two very different circumstances physiologically.[8,10]

Martin[5] showed that the 2D activation frequency in cortical bone is equal to the 3D origination frequency (which he called the true activation frequency) multiplied by the BMU's range, or the distance it traveled during its lifespan. The purpose of this study is to derive an equivalent relationship between origination frequency (Or.f) and activation frequency (Ac.f) in cancellous bone.

Methods

Due to methods in bone labeling, the formation period (FP; days) is the primary unit of time calculated from histologic slides. The erosion period (EP; days), quiescent period (QP; days), and total remodeling period (Tt.P; days) are calculated using the formation period and assuming a steady state so that "fractions of space are equivalent to fractions of time"[9]:

$$\frac{X \text{ period}}{\text{Formation period}} = \frac{X \text{ surface}}{\text{Osteoid (forming) surface}} \quad (1)$$

This results in the equations:

$$\text{QP (days)} = \text{FP} \times (\text{QS/OS}) \quad (2a)$$

$$\text{EP (days)} = \text{FP} \times (\text{ES/OS}) \quad (2b)$$

$$\text{Tt.P (days)} = \text{FP} \times (\text{BS/OS}) \quad (2c)$$

where ES, OS, QS, and BS are, respectively, erosion, osteoid, quiescent, and total bone surface areas (square millimeters). It is important to mention here that, like the time periods, these variables are not independent measurements and are typically expressed in the ratios ES/BS, OS/BS, and QS/BS.

The activation frequency is defined as 1/Tt.P, so that by combining Equations 2b and 2c we can express Ac.f as:

$$\text{Ac.f (1/day)} = \frac{1}{\text{Tt.P}} = \frac{1}{\text{FP}} \times \frac{\text{OS}}{\text{BS}} = \frac{1}{\text{EP}} \times \frac{\text{ES}}{\text{BS}} \quad (3)$$

If we continue to assume that remodeling is in a steady state, then we can approximate the eroded surface in a bone sample with the number of BMUs (NBMU) and the erosion period:

$$\text{ES (mm}^2\text{)} = \text{NBMU} \times \text{BMU.Wi} \times \text{BMU.R} \times \text{EP} \quad (4)$$

where BMU.Wi is the width of the BMU (mm) and BMU.R is the rate of BMU progression across the surface (mm/day, see Figure 1). If we substitute Equation 4 into Equation 3 and solve for NBMU we get:

$$\text{NBMU (BMUs)} = \frac{\text{Ac.f} \times \text{BS}}{\text{BMU.Wi} \times \text{BMU.R}} \quad (5)$$

However, if remodeling is in a steady state, we can also employ the mathematics of population dynamics.[3] We therefore express the number of BMUs as the birthrate of BMUs multiplied by the average lifespan:

$$\text{NBMU (BMUs)} = \text{Or.f} \times \text{BS} \times \sigma \quad (6)$$

where σ is the BMU lifespan (days) and Or.f $\times$ BS is the birthrate of the BMUs (BMUs/day). If we now equate Equations 5 and 6 and solve for Or.f, we obtain:

$$\text{Or.f (BMUs/mm}^2\text{/day)} = \frac{\text{Ac.f}}{\text{BMU.Wi} \times \text{BMU.R} \times \sigma} \quad (7)$$

which relates the histologically measured activation frequency to the physiologic origination frequency. Equating the total distance traversed by the BMU (BMU.Ds) to the rate of progression multiplied by the lifespan gives:

$$\text{Or.f (BMUs/mm}^2\text{/day)} = \frac{\text{Ac.f}}{\text{BMU.Wi} \times \text{BMU.Ds}} \quad (8)$$

Discussion

This derivation shows that the origination frequency, or 3D birthrate, of new BMUs in cancellous bone is related to the measured activation frequency divided by the BMU width, BMU rate of progression, and BMU lifespan. Conceptually, this means that the origination frequency is equal to the activation frequency divided by the average surface of bone remodeled by one BMU during its entire lifespan.

Martin expressed the relationship between histologic activation frequency and "true" activation frequency (i.e., origination frequency) in cortical bone as[5]:

$$f_T \text{ (BMUs/mm}^3\text{/day)} = \frac{f_H}{\sigma \times \text{BMU.R}} \quad (9)$$

In converting these parameters to the more standard nomenclature the histologic activation frequency, f_H, should be expressed

as Ac.f/T.Ar, whereas the origination frequency, f_T, should be represented as Or.f $\times$ BS/TV. These symbols are more appropriate than the originally proposed Ac.f/B.Ar and Ac.f/BV, respectively, as they correctly refer to the parameters as tissue referent and differentiate between activation and origination.

It is important to note that, although equations for calculating origination frequency now exist for both cancellous and cortical bone, they are dependent on values that have not yet been measured in detail (σ, BMU.R, BMU.Wi). It has been estimated that, in adult cancellous bone, the BMU.R is around 10 μm/day and σ is approximately 3 months,[10] so that BMU.Ds = BMU.R $\times$ σ would be approximately 1000 μm. However, some very time-consuming measurements on a few remodeling sites suggest that BMU.Ds is about 2000–3000 μm.[4] These same experimental observations suggest that BMU.Wi is about 500–800 μm, or greater than five times the erosion depth.[4] Clearly, techniques need to be developed to obtain statistically reliable data for these parameters.

BMU-level remodeling analysis plays the important role of connecting knowledge of osteoclast and osteoblast function to the overall architecture and mechanical properties of bone. Expressing the origination frequency in terms of histologically measurable variables is an important step in describing remodeling at this level. Such knowledge is useful clinically as well as in elucidating the responses characterized by Wolff's law or in describing other aspects of bone adaptation.

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