

Going with the Flow: An Overview and Clinical Discussion of The Rheology of Soft Tissue Fillers, Part 1 of 2

Flow properties and the clinical behavior that these properties predict can be important factors that help clinicians refine and individualize treatment with dermal fillers.

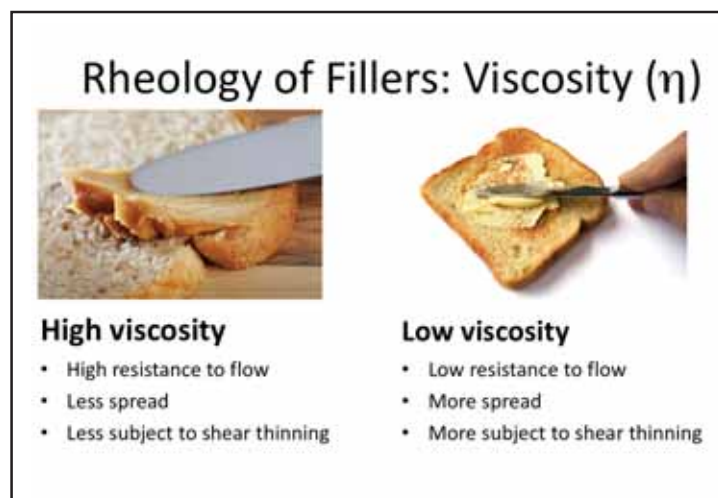
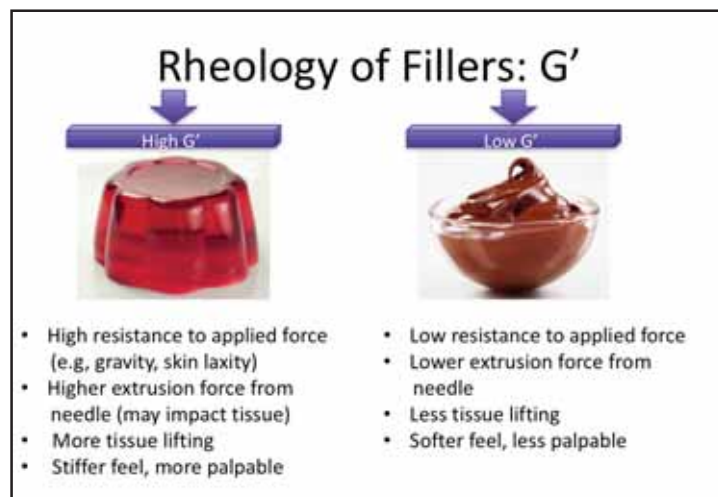
By Hema Sundaram, MD

The documented use of fillers for aesthetic purposes dates back to 1893 in Germany, when Neuber harvested a small piece of fat from the upper arm and injected it into a pitted scar on the cheek of a patient suffering from tuberculosis of the underlying bone.¹ The physician performing this autologous fat transfer procedure could scarcely have anticipated how rapidly and dramatically the vistas of soft tissue augmentation would expand over the ensuing century or so. The aesthetic use of soft tissue fillers gained momentum in 1981 with the FDA approval of injectable bovine collagen, and has soared exponentially over the past decade with the approval of several new products.

Clinicians may currently select from temporary fillers, which are chiefly cross-linked hyaluronic acid (HA) products; longer-lasting options, such as calcium hydroxylapatite (CaHA) and poly-L lactic acid (PLLA); and permanent products, exemplified by polymethyl methacrylate (PMMA). As filler options have increased, their applications have evolved. The original notion of filling individual rhytides has been largely replaced by the philosophy of volume restoration to targeted facial zones and also to non-facial areas such as the dorsum of the hands. It seems a natural transition now to consider how to achieve the desired endpoints of this volume restoration via the selection of appropriate filler products.

A recent approach to this selection process has been to study the flow-related (rheological) properties of HA and CaHA filler products, which reflect their distinct physicochemical structures. In an increasing number of presentations and publications, values obtained for the elasticity (G' or G' prime) and viscosity of specific products have been analyzed with the aim of differentiating them and predicting their behavior during and after the injection process. In a recent poster presentation² and subsequent paper, Kablik, Monheit, et al.³ provided an engaging analysis of how clinical outcomes with several commercially-available HA filler products might be correlated to the rheological properties of elasticity and viscosity, and also to other physiochemical characteristics, including HA concentration, gel-to-fluid ratio, gel concentration, particle size, gel swelling, and percentage of cross-linking. Rheology has even made its way into the general public consciousness: The last two assignments this author received to discuss the science of fillers came not from plastic surgery or dermatology conferences but from a TV station and a national newspaper.

This article, the first of two, provides a brief overview of rheological study methodology and definitions and a discussion of the value and limitations of rheological studies. The second article will present rheological data from recent studies of soft tissue fillers, discuss the potential clinical applications of



these data, and suggest some strategies for the objective evaluation of rheological studies.

Rheological Study Methodology

The basic methodology employed in rheologic studies is to place a gel between two non-deformable plates, one fixed and the other mobile. This device is known as a rheometer. The gap between the rheometer plates is adjusted so that there is complete contact between the gel and the plates. Oscillating pressure is then applied to the gel by circular rotation of the mobile plate across it at varying frequencies; this generates a variable shear force. Measurements of elasticity and viscosity are obtained at different oscillation frequencies, which correspond to different levels of shear force.

Rheometric testing can be performed on HA and CaHA filler products, since they are all defined as biphasic gels, by virtue of their containing a solid (particulate) phase suspended in a fluid phase. It is of note that products belonging to the Juvéderm (Allergan), Prevelle (Genzyme/Mentor), and Restylane/Perlane (Medicis) HA families all have a particulate and a fluid component, although particles are more prominent on ultrastructural examination for the Prevelle and Restylane/Perlane families than for the Juvéderm family. The CaHA filler, Radiesse (Merz), also comprises particulate and fluid phases.

Rheological Definitions

Elasticity is quantified as the elastic (storage) modulus, known as G' prime and often abbreviated to G' . It is a measure of the gel's stiffness and hence its ability to resist deformation under applied pressure—such as during the injection process when the filler is extruded through a needle, and after injection when the filler is subjected to movements of the facial musculature and overlying skin. The higher the G' of a gel, the less it deforms under pressure and the more energy it can retain and store. In a new paper describing rheological studies of CaHA and HA filler products,⁴ a gelatin mold is given as an example of a gel with high G' , while chocolate pudding is given as an example of a gel with low G' .

Viscosity, when quantified as complex viscosity and symbolized as η^* , measures the ability of the gel to resist shearing forces, such as may be exerted upon a filler both during and after injection. In the new CaHA /HA rheology paper,⁴ peanut butter is cited as a high viscosity gel while room temperature butter is cited as a low viscosity gel, and the shear force applied when spreading these gels on toast with a knife is discussed. Within a certain range of applied shear force, defined as the linear visco-elastic

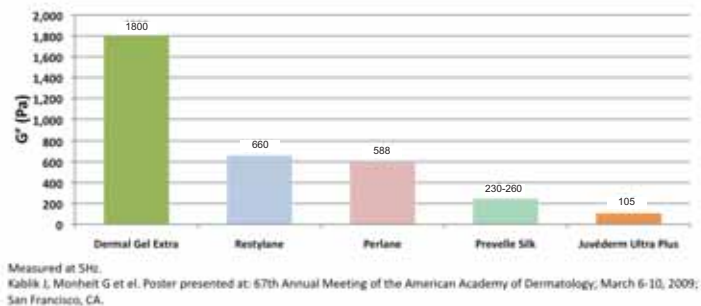
range, the gel will “thin out” (i.e., n^* of the gel will decrease) in a manner that is proportional to the applied force. This phenomenon, known as shear thinning, is controlled and predictable. If shear force is further increased beyond the linear viscoelastic range, n^* of the gel starts to decrease in an uncontrolled and unpredictable manner; this phenomenon is known as yield stress. From this point onwards, the gel no longer exhibits elastic behavior. Ultimately, if shear force is increased to a sufficiently high level beyond the linear visco-elastic range, it may actually disrupt the physicochemical structure of the gel. A high viscosity gel spreads less easily and is less susceptible to shear thinning and yield stress than is a gel of low viscosity.

Viscosity has been alternatively quantified in some studies as the viscous (loss) modulus, known as G'' and often abbreviated to G'' . This is a measure of a gel's ability to dissipate energy when shear force is applied to it and thus is reciprocally related to G' , which measures the ability of the gel to store energy. G'' is equivalent to complex viscosity (n^*) when shear force falls within the linear visco-elastic range. Some researchers consider n^* to be a more clinically relevant measurement than G'' , since they believe it gives a clearer picture of how a filler might be impacted by varying shear forces during and after injection. This may be particularly true for CaHA filler and for HA fillers with a prominent particulate component, since they behave in some respects like biphasic gels within which a third, distinctly solid phase is suspended and hence may function as multiphasic systems rather than as biphasic gels alone. G'' may not be as accurate an indicator as complex viscosity of the behavior of filler products that can display multiphasic characteristics.

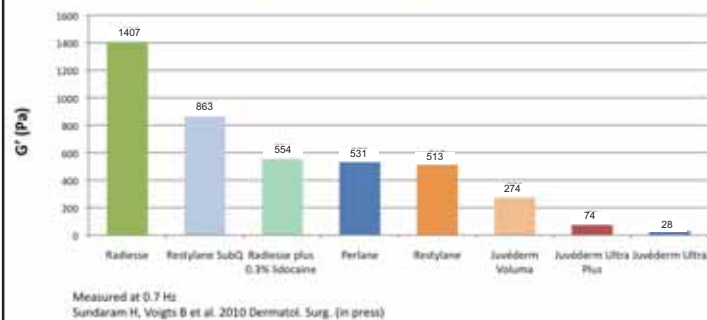
The Value of Rheological Studies

Rheological studies allow the classification of fillers whose clinical effects manifest immediately after

G' of Cross-Linked HA Fillers

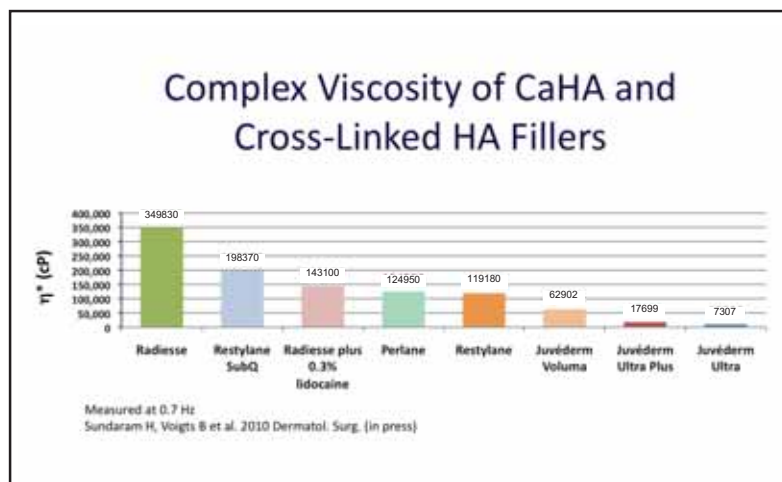


G' of CaHA and Cross-Linked HA Fillers



injection, such as HA and CaHA products, based on their measured elasticity and viscosity. This classification can be used to predict a filler's injection characteristics and its properties after injection and hence to facilitate the selection of specific filler products for the achievement of specific clinical endpoints. This strategy, known as rheological tailoring, goes beyond merely providing a scientific rationale for the gestalt that most clinicians already employ when selecting filler products.

Rheological tailoring may enable patient objectives to be met more fully and more cost-effectively by guiding the selection of different filler products to give volume-efficient lifting and stable contours



filler is subjected to force within the closed barrels of a syringe and needle and the relatively closed confines of the tissue into which it is implanted. Any findings that are clinically counterintuitive should be carefully analyzed to determine whether they genuinely reflect flow properties of the tested filler or are merely testing artifacts.

Conclusions

The array of injectable products from which today's clinicians can select to achieve specific aesthetic objectives

where needed and, conversely, to give more tissue spread where this is considered desirable. Quantification of a filler's unique flow properties can also help determine which injection techniques and implantation depths are likely to yield optimal results. This is of value to clinicians as they refine their strategies for fillers with which they are already familiar, and it can shorten the learning curve with new products. These benefits will be discussed further with specific examples in the next article.

Limitations of Rheological Studies

A major shortcoming of rheological studies is that they do not permit the analysis of two important filler products: PLLA (Sculptra, Dermik/Sanofi-Aventis) and PMMA (Artefill, Suneva). The clinical effects of these products are not related to their physicochemical structure at the time of injection but depend on the neocollagenesis that they stimulate over a period of several weeks to months after injection. Thus, their elasticity and viscosity at the time of injection do not correlate to the clinical effects that they ultimately produce.

Another limitation is that rheometric testing occurs in what is essentially a partially-open system, with the gel filler flowing between two flat plates in response to applied force. Caution must be exercised when extrapolating observations from this in vitro system to the real-life clinical situation, where the

has been compared to the palette of paints from which an artist can select when creating a beautiful picture. For two popular genres of filler—CaHA and HA—rheological tailoring allows the palette to be refined and individualized for each patient and for each facial area, based on flow properties and the clinical behavior that these properties predict. This approach is most valid when a filler's elasticity and viscosity are considered in the context of its other physicochemical characteristics such as hydrophilicity, translucence versus opacity, and degree of adjustability after implantation. Injection techniques and implantation depth of the filler should also be taken into account, since they may have a profound impact upon the results obtained. ■

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Dr. Sundaram serves as an Advisor, Consultant and/or Clinical Investigator for Medicis, Mentor/Johnson & Johnson, Merz Aesthetics and Suneva Medical. She has no stocks, shares or other financial interests in these or any other pharmaceutical companies.

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