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White Paper:

Strain Analysis – An Overview

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Version 1.1

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Table of Contents

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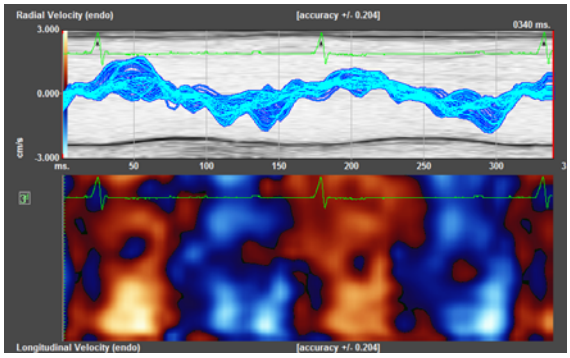
Introduction

As the field of cardiovascular research advances, scientists are becoming more sophisticated in their choice of parameters to determine heart function. Researchers are no longer content with just monitoring left ventricular function: cardiac output, fractional shortening and ejection fraction. The paradigm of biomedicine is shifting towards early detection predictors and increased sensitivity for cardiac performance. There are a variety of cutting-edge tools for biomarker assessment that have emerged in recent years, offering unprecedented insights into mechanisms and different aspects of cardiac dysfunction.

Among the plethora of methodologies available to the modern cardiologist, strain and strain rate quantification have emerged as sensitive and reproducible detectors of myocardial function and contractility,[1,2] and can be easily translatable from the preclinical to clinical research. In addition, this method is fast, easily accessible, and has a low rate of intraobserver and interobserver variability.[3] For these reasons, strain and strain analysis is likely to become the gold standard for myocardial contractility measurement, and will be an integral tool in filling the knowledge gap that currently exists in this area.[4]

Strain is a valuable tool in cardiovascular disease, cardiac regeneration, cancer therapeutics, and broader drug development areas. It can be used to sensitively monitor cardiac function and ventricular remodeling for early signs of cardiotoxicity in patients or animal models under anti-cancer therapies.[5] Given their ease of use, high reproducibility, and flexibility, it is no wonder that strain and strain rate are already being hailed as essential tools in the repertoire of any researcher interested in cardiac function.



Parametric display of segmental synchronicity analysis in normal mouse heart

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What is Strain Analysis?

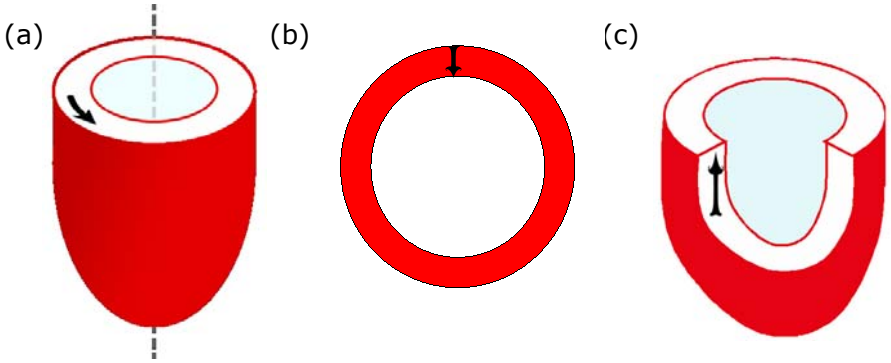
Strain analysis is based on combined speckle-tracking algorithms applied on high-frequency ultrasound images, and has been recognized as a method for angle-independent (therefore less operator-dependant) quantification of myocardial strain.[6] Strain is a dimensionless parameter that represents deformation of the heart, either regionally or globally, relative to its original shape.[3] Strain rate, as its name suggests, is simply strain per unit time. Thus, Strain (S) and Strain Rate (SR) can be represented with the following equations:[3]

$$S = \frac{\Delta L}{L_0} = \frac{L - L_0}{L_0} \qquad (1)$$

$$SR = \frac{S}{\Delta t} = \frac{(\Delta L / L_0)}{\Delta t} = \frac{(\Delta L / \Delta t)}{L_0} = \frac{\Delta V}{L_0} \qquad (2)$$

Where S is the longitudinal strain, ΔL is the absolute change in length, L_0 is the baseline length, and ΔV is the velocity gradient in the segment.

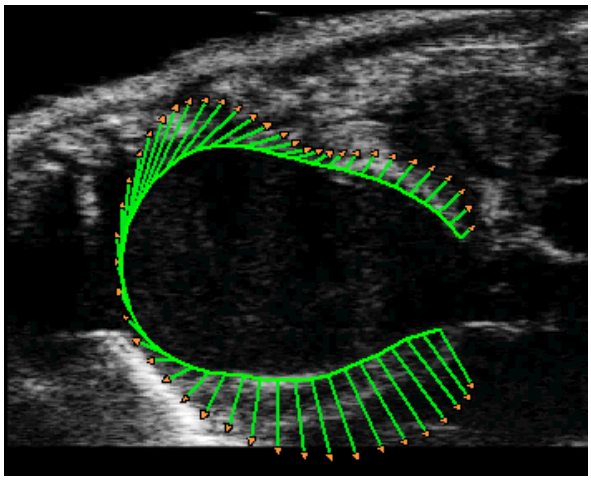
Strain is based on the estimation of velocity vectors, by tracking the pixels from the B-Mode (grayscale) images.[7] Specifically, strain algorithms track speckles, which are natural acoustics markers[8] created as a result of backscattered constructive and destructive ultrasound interference. Angle-independent velocity values are estimated by tracing a pattern on the B-Mode image that will be replicated for the number of selected cardiac cycles. Thus, strain estimates overcome limitations to other echocardiographic techniques, such as angle dependency and apical segments sampling.[4]



(a) Circumferential, (b) Radial, and (c) Longitudinal displacement of normal heart

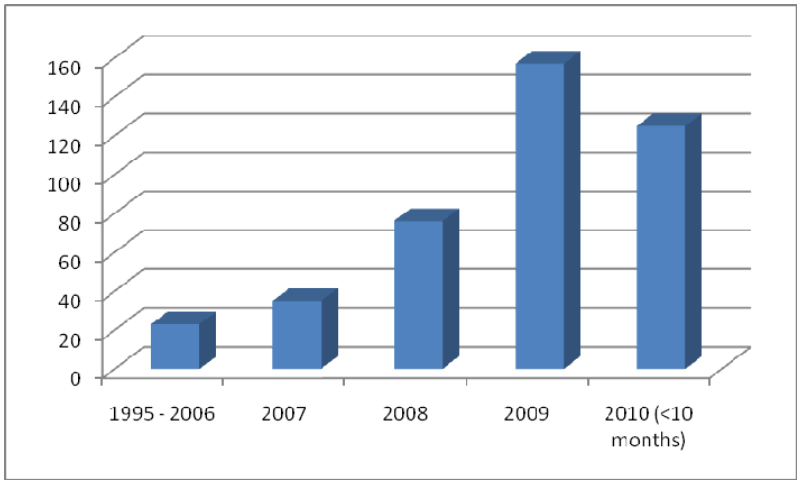
Strain differentiates between active and passive movement in the myocardium.[9] Since strain represents the stretch or shortening of tissue, longitudinal and circumferential strain represent shortening of the myocardium, and thus demonstrate negative curves.[9] On the other hand, radial strain demonstrates a positive curve because it represents a lengthening of the tissue. Together, strain and strain rate offer biomarker assessment that more accurately reflect myocardial contractile states than conventional echocardiographic measurements, such as fractional shortening and ejection fraction.[9]

Strain analysis only requires one cardiac cycle to be obtained through echocardiography. This technique is angle independent[3], the image can be post-processed and interpreted with offline software. Furthermore the data quantified can then be exported.



Why is Strain Analysis Important?

Cardiologists have long been using echocardiography to assess heart function parameters such as left ventricular (LV) function and wall-motion abnormalities. Some of these quantification tools include left ventricular ejection fraction (EF), end-systolic volume, fractional shortening (FS) and wall-motion scores. These variables are relatively easy and routine to obtain, but have severe drawbacks to the amount of relevant information they provide. For example, the ejection fractions in many patients with heart failure appear to be normal.[10] Similarly, wall-motion scores are well-known to be semi-quantitative and highly observer dependent,[11] which not only makes publishing difficult, but also limits accessibility to researchers who are not familiar with cardiology, but still wish to quantify cardiac effects of various diseases or treatments. For these reasons, strain and strain rate have been introduced as more easily measurable, reliable, and sensitive cardiac parameters. Furthermore, these technologies have been validated with magnetic resonance imaging (MRI)[12,13] and sonomicrometry,[14] making the results obtained through strain and strain rate highly publishable.



Rapid growth of PubMed citations on speckle tracking echocardiography

What can strain analysis be used for? In addition to the traditional quantifications of ventricular function, studies for biomarker assessment have also been performed in acute myocardial infarction,[11] chronic myocardial infarction,[15] cardiac dyssynchrony,[16] evaluation of ventricular torsion,[17,18] diabetes[19] and cancer therapeutic-induced cardiotoxicity.[5] Part of the reason why strain and strain rate can be used in these non-traditional cardiovascular areas is because the technique is independent of insonation angle and cardiac

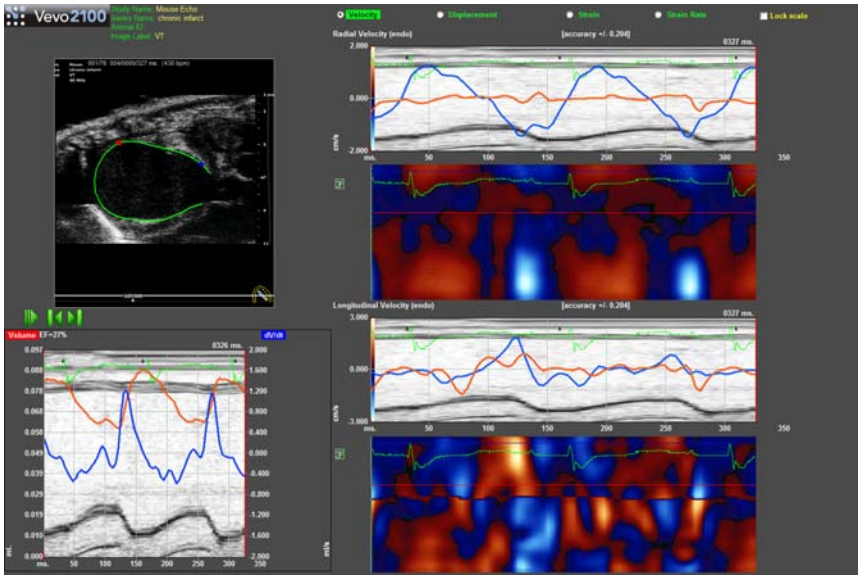
translation,[17,20,21] which makes it ideal for new users compared to other echocardiographic parameters such as Doppler flow.

There have been various studies done in the clinic to validate the use of strain and strain rate analysis. For example, it has been recently demonstrated that the technique can be used to detect regional myocardial dysfunction in patients with acute myocardial infarction.[11] It was found that nontransmural infarcted regions had decreased longitudinal function compared to noninfarcted regions, and that transmural infarcted regions had even less longitudinal function. The authors stated that strain and strain rate are superior to wall-motion score index, because of the limitations of qualitative assessment with the traditional methods.[11] Another study demonstrated that strain analysis can be also used to predict response to cardiac resynchronization therapy, by quantifying dyssynchrony and accurately predicting therapeutic response.[16] In both of the above cases, the authors concluded that this new imaging technique has tremendous potential for applications in the clinical setting.

In the preclinical and biotech / pharmaceutical fields, strain analysis is also playing integral roles in advancing research. For example, it was recently demonstrated that strain could be used to detect potential diffused myocardial impairment of the left ventricle in diabetic rats.[19] The authors concluded that strain is an easy, rapid and reproducible method that reflects intrinsic myocardial mechanics, and is thus ideal for sensitive indices such as myocardial impairment at rest.

One of the most pressing issues in oncology research is the potential cardiotoxic effects of new cancer therapeutics, such as Herceptin.[22] Myocardial dysfunction can be displayed in patients quickly, or after a long period, and may be irreversible.[5] This means that lifespan gained by the therapeutics may be offset by the cardiac dysfunction as a result. However, traditional parameters of EF and FS are insensitive to early and subtle changes in cardiac function. This is because the proportion of damaged myocardium must be enough to cause a change in global systolic function,[5] at which point damage may already be irreversible. On the other hand, strain analysis detected changes in cardiac function in children after two treatment cycles of anthracyclines, while conventional echocardiographic parameters failed to show any difference.[23] Similarly, in mice treated with doxorubicin, strain analysis

detected LV dysfunction prior to conventional indices, and was able to predict the development of late cardiac failure and mortality.[24] Thus, strain and strain rate analysis are promising biomarker assessment tools to help cancer researchers monitor sensitive and subtle changes in cardiac function, and to guide anticancer therapy and preventive measure to minimize myocardial damage in patients.[5]

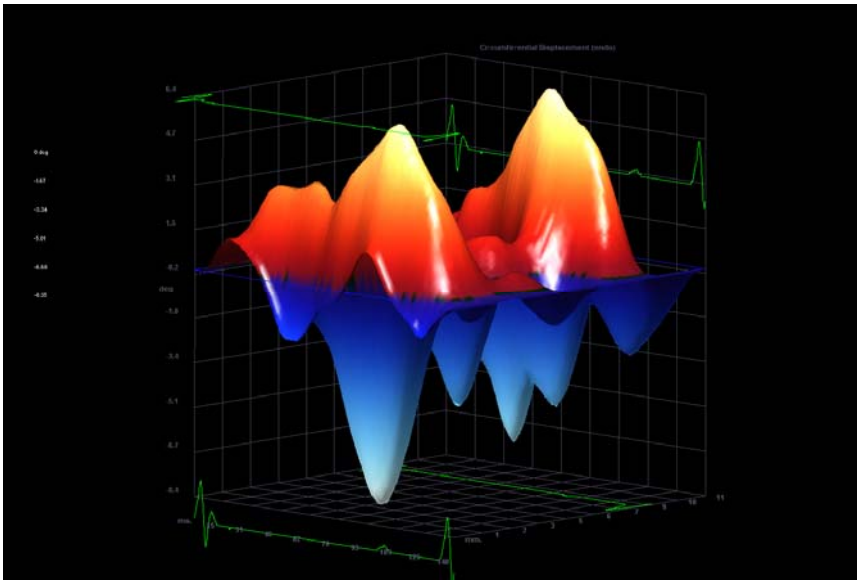


Velocity dyssynchrony analysis in a mouse infarct model

Advantages of VevoStrain™ Software

VevoStrain software is the only strain analysis software on the market that can be used to study small animals. It is designed for the Vevo® 2100 system, which is an echocardiographic machine designed specifically for preclinical research. When compared to ultrasound devices used in the human clinic, the Vevo 2100 system is able to achieve 5-10 times higher resolution at up to 30 µm, in contrast to 200-300 µm. Since strain processing software (and hence the quality of data output) is dependent on the high-resolution images acquired through echocardiography,[3] the data produced by VevoStrain software and the Vevo 2100 system are unparalleled in terms of accuracy and reproducibility.

For example, Dr. Liao's group from Harvard Medical School presented recently their work of assessing local myocardial function in ascending aortic constriction mouse hearts with the VevoStrain software.[25] The authors found that conventional methods for assessment of cardiac function are not sensitive enough to detect small changes. VevoStrain software is easy to use and sensitive for cardiac changes, providing a valuable tool to research a variety of cardiovascular disease models, including but not limited to right-ventricular heart failure, diastolic dysfunction and vessel stiffness.[25]



3D parametric display of strain and strain rate with the VevoStrain software

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