VIEWPOINT

Arrhythmia triggers in heart failure: The smoking gun of $[Ca^{2+}]_i$ dysregulation

Gary L. Aistrup, PhD,* C. William Balke, MD,† J. Andrew Wasserstrom, PhD*

*From the *Departments of Medicine (Cardiology) and the Feinberg Cardiovascular Research Institute, Northwestern University Feinberg School of Medicine, Chicago, Illinois, and †The Clinical and Translational Science Institute and Department of Medicine, University of California San Francisco, San Francisco, California.*

Among the most serious problems associated with heart failure is the increased likelihood of life-threatening arrhythmias. Both triggered and reentrant arrhythmias in heart failure may arise as a result of aberrant intracellular Ca cycling. This article presents some new ideas, based on recent studies, about how altered Ca cycling in heart failure might serve as the cellular basis for arrhythmogenesis.

KEYWORDS Calcium alternans; Calcium cycling; Calcium waves; Heart failure

ABBREVIATIONS **APD** = action potential duration; **AR** = alternans ratio; **DAD** = delayed afterdepolarization; **HF** = heart failure; **MPT** = mitochondrial permeability transition pore; **NCX** = Na-Ca exchanger; **RyR** = ryanodine receptor; **SERCA2a** = sarcoplasmic/endoplasmic reticulum Ca-ATPase; **SHR** = spontaneously hypertensive rat; **SR** = sarcoplasmic reticulum; **TWA** = T-wave alternans

(Heart Rhythm 2011;8:1804–1808)

Introduction

The incidence and prevalence of heart failure (HF) has steadily increased over the last 25 years in spite of the overall decline during the same period in the age-adjusted death rates for cardiovascular diseases in general.[1] As of 2006, the incidence of HF was estimated at 660,000 new cases per year, and the prevalence of HF was approximately 5.3 million patients, or 2.5% of the total United States population.[1] The incidence of new cases of HF increases dramatically with age and spares neither gender nor race. On the basis of the 44-year follow-up of the original Framingham Heart Study cohort and the 20-year follow-up of the offspring cohort, the lifetime risk of developing HF in men and women is staggering at 1 in 5 individuals.[1,2] Of those individuals younger than 65 years, 80% of men and 70% of women will die within 8 years, and the 1-year mortality is extraordinarily high at 1 in 5. Consequently, overall deaths from HF have failed to decline from 1993 to 2004.

HF represents the final stage of a variety of cardiac diseases, with hypertensive heart disease being the most common. The two major causes of death in HF patients are mechanical pump failure and electrical abnormalities leading to cardiac arrhythmias, with the incidence of sudden cardiac death being 6 to 9 times greater in HF patients compared with the general population. In light of these alarming statistics, it is not surprising that the number of HF-related hospital discharges increased by 171% from 1979 to 2005, and that the estimated direct and indirect costs of HF in the United States for 2008 is $34.8 billion.[1] Clearly, our current preventive and therapeutic HF strategies have failed to reverse this epidemic proportion of HF and to lessen the human and economic costs of HF on our society.

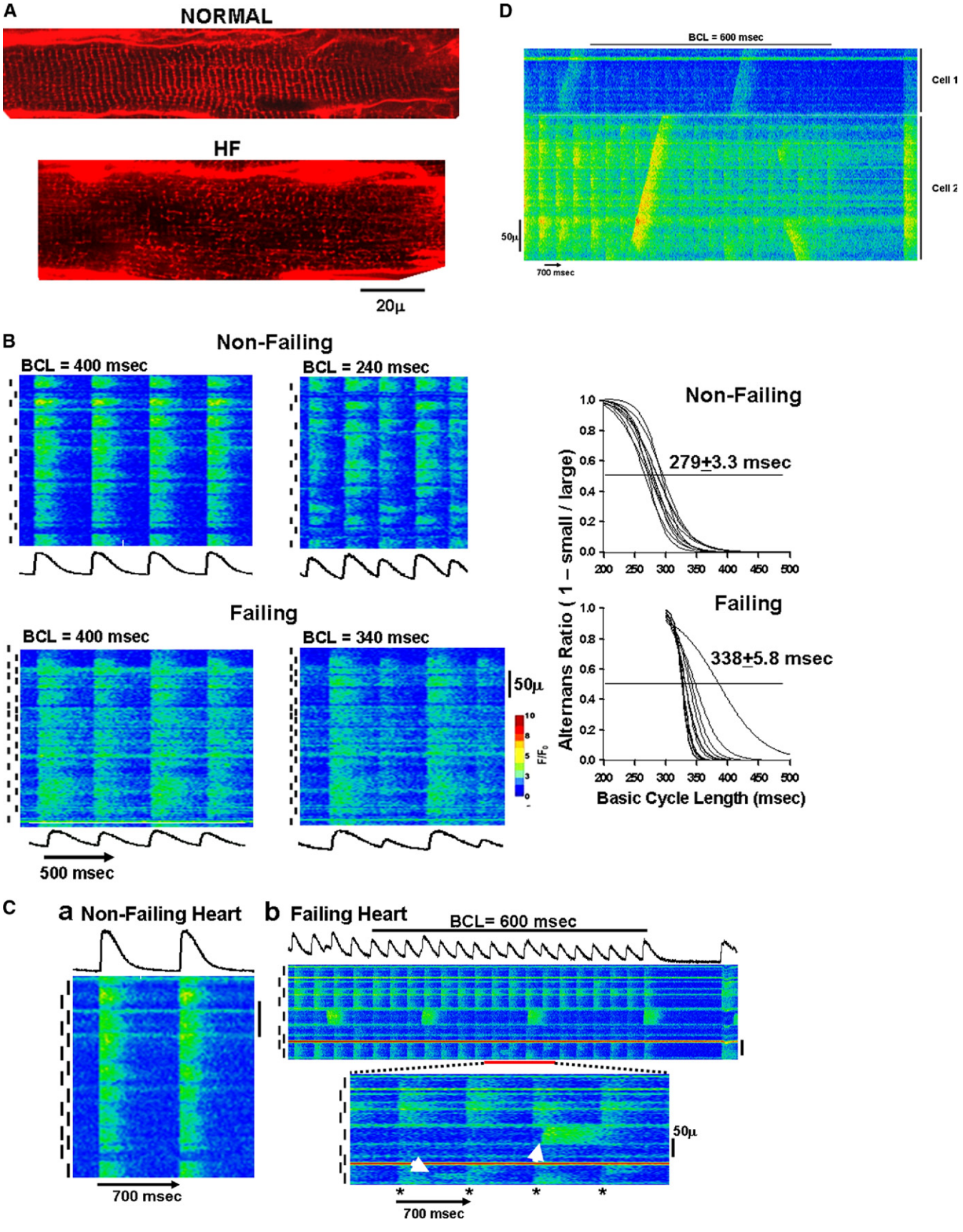
Unfortunately, the precise mechanisms that underlie the contractile and electrical abnormalities characteristic of HF remain elusive in spite of decades of intensive clinical and basic science investigations. Progress has been slowed, in part, by the sheer complexity of the HF phenotype, which represents the intersection of a multitude of physiological, neurohumoral, and biochemical abnormalities that are themselves the consequences of the interplay of multiple and complex genetic and environmental influences. However, recent clinical studies and studies of relevant animal models of hypertensive heart disease show promise in identifying dysregulation of intracellular Ca handling as a unifying mechanism for both the contractile and electrical abnormalities seen in HF.

Defects in cellular Ca handling in HF

Over the years, numerous changes in Ca handling have been identified in many experimental models of HF and in failing human hearts. The most consistent and significant abnormality in Ca handling is fragmentation of the normally synchronous release of Ca from the sarcoplasmic reticulum

Address reprint requests and correspondence: Dr. J. Andrew Wasserstrom, Northwestern University Feinberg School of Medicine, 310 E Superior St, Morton 7-607, Chicago, IL 60611. E-mail address: ja-wasserstrom@northwestern.edu.

1547-5271/$ -see front matter doi:10.1016/j.hrthm.2011.06.012


A
NORMAL
HF
20μ
D
BCL = 600 msec
Cell 1
Cell 2
50μ
700 msec
B
Non-Failing
BCL = 400 msec
BCL = 240 msec
Failing
BCL = 400 msec
BCL = 340 msec
50μ
F/F0
500 msec
Non-Failing
279±3.3 msec
Failing
338±5.8 msec
Alternans Ratio (1 – small / large)
Basic Cycle Length (msec)
C
a Non-Failing Heart
700 msec
b Failing Heart
BCL= 600 msec
50μ
700 msec