Transmural Electrophysiological Heterogeneities Underlying Arrhythmogenesis in Heart Failure

Fadi G. Akar, David S. Rosenbaum

Abstract—Although expression of numerous ion channels is altered in heart failure (HF), mechanisms by which dysfunction at the ionic and molecular levels lead to ventricular tachyarrhythmias in HF are unknown. Previously, we found that transmural heterogeneities of repolarization play a critical role in the genesis of polymorphic ventricular tachycardia (PVT) when QT interval was prolonged in LQT2. Because QT interval is also prolonged in HF, we hypothesized that transmural heterogeneities are a mechanism of PVT in HF. Optical action potentials were measured simultaneously from cells spanning the entire transmural wall of arterially perfused canine wedge preparations. Wedges were isolated from dogs without (control, n=5) and with HF (n=8) produced by rapid ventricular pacing. In HF, action potential duration (APD) prolongation was markedly heterogeneous across the transmural wall, and was characterized by disproportionate APD prolongation of midmyocardial (M) cells. APD prolongation of M cells accounted for QT-interval prolongation, and caused significant increases (P<0.01) in spatial gradients of repolarization across the ventricular wall from 4.3±2.1 (control) to 12.4±3.5 ms/mm (HF). Enhanced gradients were directly responsible for development of functional conduction block, leading to PVT in 63% of HF wedges but in no controls (P<0.03). Moreover, intramural decremental conduction and block of the premature impulse, preceded each episode of PVT, and always occurred at the border between M-cell and subepicardial zones, where repolarization gradients were highest. Selective prolongation of APD within M cells underlies several key features of the HF phenotype, including QT-interval prolongation, transmural heterogeneity of repolarization, and susceptibility to conduction block and reentrant PVT. (Circ Res 2003;93:638-645.)

Key Words: heart failure ■ long-QT syndrome ■ repolarization ■ action potentials ■ arrhythmias

Ventricular arrhythmias leading to sudden cardiac death (SCD) account for ≈50% of deaths in patients with congestive heart failure (HF). Recent investigations have markedly advanced our understanding of the molecular and ionic alterations that occur in response to HF in both humans and animal models. However, mechanisms by which HF-induced changes at the cellular and molecular levels form a substrate for life-threatening ventricular arrhythmias remain poorly understood.

Although many discrepancies regarding the specific ionic and molecular processes in HF have been reported, a consistent finding is prolongation of cardiac repolarization. This may be attributed to functional downregulation of outward potassium currents and/or upregulation of inward calcium or late sodium currents in hypertrophied and failing hearts. However, the relationship between alterations of repolarization and arrhythmia mechanisms in HF remains largely unknown. Previously, we found that transmural heterogeneities of cellular repolarization play a critical role in the genesis of the polymorphic ventricular tachycardia (PVT) Torsade de pointes when QT interval was prolonged in a model of LQT2. We hypothesized that similar heterogeneities are enhanced in HF and play a significant role in the mechanism of PVT.

To investigate transmural heterogeneities of cellular repolarization and their potential role in HF-related arrhythmias, we utilized the technique of transmural optical imaging. This allowed the measurement of action potentials simultaneously from cells spanning the entire transmural wall of the arterially perfused canine wedge preparation. We demonstrate that heterogeneous and selective prolongation of repolarization between cell types across the ventricular wall underlies an electrophysiological mechanism for unidirectional block, reentry, and PVT in HF.

Materials and Methods

Transmural Optical Action Potential Mapping

We designed a system capable of simultaneously recording action potentials with high spatial (0.7 to 1.2 mm), temporal (0.5 ms), and voltage (0.5 mV) resolutions from cells spanning the entire...
end-stage HF in all dogs, as manifested by anorexia, lethargy, ascites, tachypnea, and muscle wasting. The presence of significant LV systolic dysfunction (LVEF 0.30 to 0.35) was documented by 2-dimensional echocardiography in every animal. Because the location in the heart from which wedges are isolated influence the functional topographical distribution of cell types across the transmural wall, we consistently selected wedges from midapicobasal regions of the anterior LV free wall.

Experimental Protocol
Electrophysiological heterogeneity across the transmural wall was assessed by recording 256 optical action potentials simultaneously from across all myocardial layers of the transmural LV wall during steady-state endocardial pacing (2× diastolic threshold) over a wide range (300 to 5000 ms) of basic cycle lengths (BCL). To assess changes in susceptibility to and the mechanism of arrhythmias in HF, programmed electrical stimulation was performed using an identical protocol on all control and HF preparations. After a 20-beat drive-train at a BCL of 2000 ms, an epicardial premature stimulus (S2) was delivered at S1S2 coupling interval of 500 ms. S1S2 interval was sequentially shortened by 10 ms decrements until refractoriness was reached or an arrhythmia was induced.

Data Analysis
Activation times, repolarization times, and action potential durations (APD) were measured directly from all optical action potentials using previously validated algorithms. Cells were classified as epicardial, midmyocardial, or endocardial according to previously established criteria. Transmural patterns of APD are displayed as contour maps, and the maximum spatial gradient of repolarization (∇Rmax) across the transmural wall was calculated in control and HF wedges using previously described algorithms. Differences in susceptibility to ventricular tachycardia (VT) between control and HF wedges were compared using the Fisher Exact test. All other comparisons were made using the Students t test. Summary data are presented as mean±SD. Differences were considered significant at P<0.05.

Results
Electrophysiological Properties of Failing Myocardium
The canine wedge model of HF exhibited several structural and electrophysiological changes characteristic of HF in humans. As evident in Figure 1A, HF wedges exhibited significant (P<0.001) LV wall thinning, consistent with other animal models of rapid pacing induced dilated cardiomyopathy. On average, ventricular wall thickness was reduced by 46%. In this model, wall thinning was relatively uniform across the LV. Also shown in Figure 1B, right, is the extent of QT-interval prolongation (by 38%, P<0.001) in this model of HF. In addition to the aforementioned structural and ECG changes, transmural optical mapping in HF wedges revealed important electrophysiological changes at the cellular level. Shown in Figure 1B, left, are representative action potentials recorded from the epicardial layer of a control (top) and HF (bottom) wedge. Epicardial APD in the HF wedge was prolonged significantly (by 23%, P<0.001). Optical action potentials recorded from the epicardial layer of HF wedges lacked the distinctive epicardial spike and dome morphology of control hearts (Figure 1B), confirming earlier findings regarding downregulation of Im in both human and canine HF.

As shown in Figure 2, although PVT could not be induced by single premature stimuli in controls, PVT was induced in...
63% of HF wedges ($P < 0.03$) using the identical stimulation protocol. Arrhythmias induced in this model were characterized by a polymorphic, undulating ECG morphology (Figure 2, bottom) and typically self-terminated within several seconds. The average cycle length of PVT was 134 ms.

### Figure 2.

**Figure 2.** QT interval, percent incidence of PVT, and representative episodes of PVT in canine wedge model of HF. HF wedges exhibited a significant prolongation of QT interval, which was associated with a marked increase ($P < 0.03$) in arrhythmia inducibility with a single premature stimulus. Arrhythmias induced in HF wedges were polymorphic in nature, had an average CL of 134 ms, and typically spontaneously terminated within a few seconds. CL indicates cycle length.

### APD Heterogeneities in Failing Myocardium

Shown in Figure 3 are transmural APD contour maps and selected subepicardial, midmyocardial, and subendocardial action potentials from representative control (left) and HF (right) wedges. In control, the shortest APDs (dark blue contours) occurred in epicardial and subepicardial layers, whereas the longest (light blue contours) invariably occurred in deep midmyocardial layers that closely juxtaposed (1 to 4 mm) the endocardial border. Although all myocardial cell layers exhibited significant APD prolongation in HF, such prolongation was markedly heterogeneous. In particular, APD prolongation of midmyocardial (M) cells was substantially greater than epicardial cells, causing a significant rise (by 109%) in the transmural APD gradient. Overall, HF-induced a significant ($P < 0.001$) rise (from 4.3±2.1 to 12.4±3.5 ms/mm) in $\nabla R_{\text{max}}$, which was consistently located at the interface between epicardial and M cells. Because total activation time was relatively fast, transmural dispersion of repolarization was driven primarily by APD gradients.

Shown in Figure 4 is a summary from all experiments of the extent of HF-induced APD prolongation in all cell layers spanning the transmural wall. HF-induced APD prolongation was relatively minor ($\approx 50$ ms) in subepicardial layers, but was markedly increased in deeper myocardial layers. As shown in Figure 4, the greatest degree of APD prolongation consistently occurred in midmyocardial layers (ie, M cells) adjacent to the endocardial border. Furthermore, midmyocardial muscle layers uniformly exhibited the longest APD in both control and failing wedges. Interestingly, the average QT-interval prolongation caused by HF ($\approx 70\%$, Figure 4, dashed lines) exceeded the average APD prolongation of both...
epicardial and endocardial cells. In contrast, APD prolongation of M cells residing in deep muscle layers was essentially identical to QT-interval prolongation and, hence, was the most likely explanation for QT-interval changes observed in HF (Figure 4).

Figure 5 illustrates the average rate dependence of APD in epicardial, midmyocardial, and endocardial layers of control and HF wedges. APDs of cells in all myocardial layers increased as BCL was slowed. In control and HF dogs, APD reached an apparent steady-state value at 2000 ms BCL, above which, relatively minor changes in APD occurred regardless of cell type. In control, the difference in steady-state APD between M and epicardial cells was ~50 ms. This difference was relatively preserved at slower BCLs, but was markedly attenuated at faster ones (Figure 5). In HF, the extent of APD prolongation was less pronounced at fast BCLs compared with slower ones, but was always greater than controls regardless of rate. Importantly, APD prolongation in HF was markedly heterogeneous as M and endocardial cells underwent a more enhanced prolongation of their APD compared with epicardial cells, accounting for an increased APD gradient (100 ms) between epicardial and midmyocardial cell layers (Figure 5, filled diamonds and filled circles, respectively). In contrast, differences in APD between midmyocardial and endocardial cells were relatively minor at all BCLs tested. Finally, in HF, APD of endocardial and M cells exhibited significantly more enhanced sensitivity to rate as compared with epicardial cells (Figure 5). The BCL-dependence of APD for epicardial, M, and endocardial layers of control and HF preparations were each fit to a single exponential function. Interestingly, there was a significant \( P<0.01 \) decrease in the time constant of this relationship in endocardial (307±32 ms control, 246±10 ms HF) and M (331±16 ms control, 244±29 ms HF) but not (\( P=0.7 \)) epicardial (404±26 ms control, 393±16 ms HF) layers in HF relative to controls, further illustrating that HF produces relatively selective effects on the repolarization properties of M and endocardial cells. Our data indicate that this selectivity is the underlying basis for transmural heterogeneities of repolarization associated with HF.

Arrhythmia Mechanism Underlying PVT in Failing Myocardium

To determine the role of HF-induced transmural heterogeneity of repolarization on arrhythmia vulnerability, single premature stimuli were delivered from the epicardium during steady-state pacing. Shown in Figure 6 are action potentials recorded from muscle layers spanning the entire transmural wall in representative control (left) and failing (right) wedges before and after delivery of a closely coupled premature stimulus.
HF resulted in intramural decremental conduction (sites A and B) and block (site C). Importantly, conduction block always occurred at the subepicardial-M cell interface, where the largest spatial gradients of repolarization invariably occurred. Furthermore, intramural conduction block in HF was always followed by the initiation of PVT (Figure 6).

The dependence of PVT on transmural repolarization gradients is further illustrated in Figure 7, which compares values of $\nabla R_{\text{max}}$ between preparations with (PVT+) and without (PVT−) susceptibility to block and reentrant PVT. The dashed line at $\nabla R_{\text{max}}=10 \text{ ms/mm}$ corresponds to a value found in previous studies to be required for the development of functional block in ventricular myocardium.18 It is evident that HF (filled circles) produces some variability in $\nabla R_{\text{max}}$ that is expected from the biological variability of this phenotype. However, it is also evident that HF was associated with the largest $\nabla R_{\text{max}}$. Importantly, every (100%) preparation that was susceptible to conduction block and PVT exhibited $\nabla R_{\text{max}})>10 \text{ ms/mm}$, whereas only 1 of 8 (12.5%) of preparations that were resistant to block and PVT exhibited $\nabla R_{\text{max}})>10 \text{ ms/mm}$. These data further reaffirm the dependence of susceptibility to functional block and reentry on the formation of critical transmural gradients of repolarization in HF.

Interestingly, the average coupling interval of the S2 beat at which block and PVT occurred (288±5 ms) consistently fell in a window of time when epicardial (APD=267±3 ms), but not midmyocardial (APD=368±16 ms) cells had repolarized, indicating the creation of a spatiotemporal “window of vulnerability” to reentry by HF that was absent in controls. The consistent dependence of PVT on conduction block within regions of steepest repolarization gradient, and its induction by properly timed premature stimuli strongly implicates reentrant excitation based on transmural repolarization gradients as the underlying arrhythmia mechanism.

Finally, shown in Figure 8 are activation contour maps depicting transmural patterns of wavefront propagation during a representative induction of PVT. After delivery of a single premature stimulus (S2), the activation wavefront blocked along the interface between epicardial and M cells, but continued to propagate along the epicardium. After sufficient time delay, M cells repolarized, and the impulse invaded the formerly refractory M tissue and re-excited the epicardium, which due to its inherently shorter APD was again excitable, thereby completing a full beat of reentry (Figure 8, V1). Obviously, the precise trajectory of the first reentrant wave is dependent on the specific topography of M cells in each heart. However, the same general pattern appeared consistent in each case. Because of rapid rate adaptation of M-cell APDs,6 the zone of block collapsed into lines of functional block as reentrant rotors formed deep in the myocardium out of the mapping field (Figure 8, V2).

Discussion

Sudden cardiac death due to ventricular tachyarrhythmias is a major cause of mortality in patients with HF. Although recent investigations have appreciably advanced our understanding of the molecular and ionic changes that occur in hypertrophied and failing hearts, mechanisms by which ion channel dysfunction leads to functional electrical instability and arrhythmias at the tissue and organ levels remain poorly understood.

Previous studies have highlighted the importance of potassium channel downregulation,2,3 late sodium current activity,7 and altered calcium homeostasis8 in the pathophysiology of HF. These changes at the cellular level have indirectly implicated a potential role for triggered activity and reentry in the mechanism of arrhythmias in HF. However, because of limitations of conventional recording techniques in intact multicellular preparations, an integrated understanding of the mechanistic relationship between alterations of ion channel function and arrhythmias in HF remained elusive.

QT-interval prolongation is a well-recognized feature of human and experimental HF.2,3 Previously, we found that enhanced transmural electrical heterogeneities of repolariza-
tion are causally related to arrhythmia vulnerability when QT interval is prolonged in an experimental model of LQT2. Hence, we hypothesized that similar mechanisms (ie, enhanced transmural heterogeneities) may be responsible for arrhythmogenesis in the failing heart. To that regard, high-resolution transmural optical action potential mapping was performed in the canine wedge preparation. This approach allowed for the first time, a detailed and simultaneous measurement of cellular repolarization across the transmural wall in an intact preparation, where the influence of cell-to-cell coupling was present; thereby providing a novel and quantitative assessment of transmural dispersion of repolarization in HF. We provide direct evidence that HF-induced electrophysiological changes preferentially target M cells, and have relatively less influence on epicardial cells. Our data further suggest that relatively selective prolongation of APD within M cells may underlie key features of the HF phenotype, including QT-interval prolongation, transmural heterogeneity of repolarization, and susceptibility to conduction block and reentrant arrhythmias.

Transmural Heterogeneities of Repolarization in Heart Failure

Using transmural optical mapping, fundamental differences in the properties of action potentials recorded from control and failing hearts were evident. Consistent with findings in isolated myocytes, optical action potentials of failing hearts exhibited a pronounced reduction in spike and dome morphology, indicating downregulation of $I_{Kr}$ (Figure 1). Furthermore, APD in HF wedges was significantly prolonged relative to controls, but to a lesser extent than that reported previously from isolated myocytes. These differences were likely attributable to artifactual changes associated with the myocyte isolation procedure, high level of intracellular calcium buffering, and lack of intercellular coupling in isolated myocytes.

In this study, the topographical distribution of different cell types, and the magnitude and orientation of the transmural APD gradient in HF were reported for the first time. In controls, epicardial and subepicardial cells displayed the shortest APDs, whereas M cells displayed longer ones, despite presence of cell-to-cell coupling in the wedge preparation (Figure 3). Whereas epicardial cells underwent relatively modest (~50 ms) APD prolongation in HF, M-cell APDs were prolonged more markedly. HF-induced heterogeneous prolongation of APD across the ventricular wall resulted in a 2-fold increase in the transmural APD gradient at the interface between epicardial and M cells (Figure 3). Therefore, these data provide evidence that HF-induced remodeling greatly enhances spatial dispersion of repolarization across the transmural LV wall.

Early reports have suggested indirectly that transmural dispersion of repolarization is a component of the electrophysiological substrate in HF. Analysis of standard 12-lead ECGs on HF patients showed a significant increase in interlead QT dispersion (QTd). Also consistent with our findings, selective prolongation of APD in subendocardial relative to subepicardial cells was demonstrated using floating microelectrode recordings in a rabbit model of LV hypertrophy. However, there are recent data suggesting that nonuniform APD prolongation in myocytes isolated from transmural layers of the LV in the canine tachycardia pacing HF model can result in a reduction of transmural APD gradients. Contrary to our present findings, APD prolongation was more pronounced in cells isolated from muscle layers adjacent to the endocardium and epicardium than those from the mid-wall. This discrepancy may be due to several factors inherent to isolated myocyte recordings but not optical mapping, including the influence of artificial calcium buffering, enzymatic dissociation procedures used in that study on various muscle layers, or absence of intercellular connections and the extracellular matrix. Moreover, we previously found that the topographical distribution of M cells is complex and is not limited to the central portion of the ventricular wall, but often penetrates to within thin (~1 mm) layers of the endocardium or epicardium. Hence, a detailed investigation of transmural dispersion of repolarization requires measurement of APDs with high spatial resolution from all cell layers, so as to avoid misclassification of various cell populations.

A number of factors are likely to contribute to the selective enhancement of APD and APD rate-dependence of M and endocardial cells, which in the present study were a consistent characteristic of failing myocardium. To date, numerous investigations have highlighted the importance of potassium current downregulation in HF. For example, reduction of $I_{Kr}$ density in human HF correlated with marked attenuation of the action potential phase-1 notch amplitude and prolongation of APD. However, more recent studies have suggested that changes in $I_{Kr}$ can only influence APD when intracellular calcium is artificially buffered. Our data suggest that APD prolongation and, more importantly, the substrate for arrhythmias in HF is not related to downregulation of $I_{Kr}$ because cells possessing the greatest density of $I_{Kr}$ (ie, epicardial cells) were most resistant to HF-induced APD prolongation. Remodeling of the slowly ($I_{Ks}$) and rapidly ($I_{Kr}$) activating components of the delayed rectifier K current have been reported in a rabbit model of pacing-induced HF. Because heterogeneities in $I_{Kr}$ exist across the transmural wall, one would expect that changes in $I_{Kr}$ or $I_{Ks}$ in response to HF to alter the normal distribution of APD. Our data demonstrate that APD gradients in HF are qualitatively similar to those observed in a model of acquired LQT2, and hence support the notion that a functional downregulation of $I_{Kr}$ may play an important role in HF-induced arrhythmogenesis. Also, we cannot rule out overexpression of inward currents or alterations in calcium handling proteins as a mechanism of HF-induced APD gradients, as there is recent evidence for transmural heterogeneity in cellular $I_{Ca-L}$, $I_{Ca-T}$, $I_{Ca-L}$, and calcium cycling.

In addition to HF-induced alterations in ion channel expression and function, downregulation and redistribution of gap junction proteins is a prominent feature of human and animal models of HF. Reduced coupling between muscle layers can unmask the intrinsic electrophysiological heterogeneities present at baseline. Therefore, it is conceivable that changes in gap junction expression and function, inde-
A major advantage of high-resolution transmural optical mapping is the ability to determine the topographical distribution, and not just the magnitude of the APD gradient across the ventricular wall. As illustrated in Figure 3, M cells (shown in red) were present in deep myocardial layers that closely (1 to 2 mm) abutted the endocardium. The M-cell layer was generally oriented parallel to the endocardial and epicardial surfaces in wedges isolated from the anterior wall of the LV. Previously, we found that M cells constitute more complex island-like topographical distributions in preparations isolated from other regions of the heart, including the lateral LV free wall, and hence may be subject to alternative HF-induced remodeling. Further investigation of regional differences in HF-induced APD changes is, therefore, required.

**Cellular Basis Underlying QT-Interval Changes in Heart Failure**

In HF wedges, the QT interval was markedly prolonged compared with controls. Interestingly, the degree of QT-interval prolongation exceeded that of epicardial APDs, indicating that it could not be explained by APD changes on the epicardium. In contrast, the selective APD prolongation of M cells was comparable to and, therefore, most likely underlies QT-interval prolongation in HF (Figure 4). Previously, it was shown that final repolarization of M cells provided an electrophysiologic basis for the QT interval under normal circumstances and in long-QT syndrome (LQTS). The present data extend these findings to HF.

Our findings may also explain the heretofore poorly understood observation of enhanced beat-to-beat QT variability (“QT dynamicity”) that is associated with worsened prognosis in HF. Our data suggest that in HF, myocytes within M-cell layers determine the QT interval (Figure 4) and display the greatest degree of APD responsiveness to heart rate (Figure 5), thereby, potentially explaining why temporal variability of the QT interval is greater in HF. Enhancement of QT dynamicity by a steeper M compared with epicardial and endocardial APD restitution relationship in HF could also promote concordant and discordant repolarization alternans. Steeper M-cell APD restitution may in fact contribute to arrhythmogenesis in this model by independently enhancing dispersion of repolarization via a discordant alternans mechanism, or by resulting in scroll wave meander, which potentially may explain the polymorphic (rather than monomorphic) nature of these arrhythmias. In humans, steep M-cell APD restitution in HF may promote reentrant wave break-up leading to the degeneration of PVT into persistent ventricular fibrillation (VF). 

**Reentrant Mechanism of Ventricular Arrhythmias in Heart Failure**

Arrhythmias induced in this model of HF exhibited a polymorphic undulating ECG morphology and were only initiated in cardiomyopathic ventricles (ie, not in controls) exhibiting a prolonged QT interval. Clinically, VT/VF in patients with dilated cardiomyopathy is often sustained, leading to hemo-dynamic collapse and death. The relatively confined muscle mass of the canine wedge preparation, however, most likely explained the spontaneous termination of polymorphic VT in these preparations by annihilation of reentrant wavefronts along tissue boundaries. In our experiments, polymorphic VT did not initiate spontaneously. Rather, a premature stimulus was required to initiate the arrhythmias. Furthermore, because these arrhythmias were consistently and reproducibly induced by single premature stimuli, and were dependent on intramural conduction block caused by steep transmural gradients of repolarization, they were most certainly due to reentrant excitation. Previous studies in isolated myocytes and Purkinje fibers have demonstrated an enhanced susceptibility of such preparations to development of triggered activity and enhanced automaticity when isolated from failing hearts. These preparations, however, lack cell-to-cell coupling, which is expected to alter the threshold for EAD- and DAD-mediated triggered beats in intact myocardium, such as the canine wedge and the whole heart.

It is important to emphasize that in patients with nonischemic cardiomyopathy, responses to programmed cardiac stimulation are poorly predictive of spontaneous arrhythmic events. Therefore, our results should not be taken to suggest that the animals studied were at higher risk for spontaneous arrhythmias. There are also several obvious differences between isolated perfused wedges of dog myocardium and patients with HF, including lack of autonomic input, a slower and fixed heart rate, and potential differences in substrate compared with coronary disease. Therefore, our results should be extrapolated with caution to patients with HF. Because of the unpaired nature of this study, an important aspect of our experimental design was to compare similar regions of normal and HF ventricles. In so doing, we limited our analysis to a region from which viable wedge preparations could be consistently harvested in all hearts. Hence, we cannot determine from our data whether comparable repolarization gradients are present everywhere in the heart. However, HF-induced remodeling altered repolarization sufficiently to produce arrhythmias in the region studied. Because the dimensions of reentrant circuits in human VT are on the same size-scale as the wedge preparation, functional alterations of repolarization in these preparations could indeed account for sustenance of arrhythmias at the level of the whole heart.

Finally, these data motivate future investigations of the molecular bases underlying enhanced transmural dispersion of repolarization in HF. Specifically, this report suggests that differences underlying remodeling of epicardial and M-cell repolarization properties in HF may be a critical link to a more comprehensive understanding of the mechanism of arrhythmias in failing myocardium. Such mechanisms may involve HF-induced alterations in ion channel and gap junction function and expression occurring at the molecular level. Identifying mechanisms underlying HF-induced remodeling constitutes an important step toward the development of new strategies for its prevention and treatment.

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References


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