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Drug-induced arrhythmias and sudden cardiac death: implications for the pharmaceutical industry

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Following a series of high profile withdrawals from the market, the ability of medications to induce potentially fatal arrhythmias is a significant problem facing the pharmaceutical industry. Current preclinical cardiac safety assays are based on the assumption that blockade of a single repolarizing K^+ channel alone precipitates drug-induced arrhythmias, however, current findings point to a range of more complex arrhythmogenic mechanisms. This review begins by exploring clinical findings and potential mechanisms underlying drug-induced sudden cardiac death and then goes on to assess current and explore future strategies to detect cardiotoxicity at the preclinical stage.

Introduction

When corrected for heart rate, the QT interval on an electrocardiogram (ECG) is a direct marker of ventricular action potential duration (APD) and represents the time taken for the heart to return to a resting state following the preceding contraction that pumps blood around the body (Fig. 1a). The cardiac action potential represents the combined, coordinated activity of a range of inward and outward ionic currents. Rapid influx of extracellular Na^+ (I_{Na}), mediated by voltage-gated Nav1.5 channels and contributing to phase 0 of the action potential, is immediately followed by a transient repolarization phase (I_{to}, phase 1) controlled by Kv1.4 and Kv4.2/Kv4.3 channels [1]. Shortly thereafter, the opening of sarcolemmal L-type Ca^{2+} channels, encoded by Cav1.2, leads to Ca^{2+} influx ($I_{Ca,L}$) and calcium-induced calcium release from the sarcoplasmic reticulum, a process-mediating contraction of the myocyte and mechanical systole throughout the myocardium. The complex process of terminal repolarization of the action potential (phase 3) is delicately controlled by a variety of K^+ channels, particularly the rapid (Kv11.1) and slow (Kv7.1) components of the delayed rectifier channels, known as I_{Kr} and I_{Ks} and encoded by the HERG and KCNQ1 genes, respectively (Fig. 1b) [2]. It is now widely acknowledged that there is a degree of redundancy in outward repolarizing K^+ currents in the human heart, particularly in the ventricle [3]. The term 'repolarization reserve' was coined to describe this redundancy and explain why lesions in a single outward K^+ current, for example I_{Ks}, often yield little or no delays in repolarization [4]. If one superimposes upon this, however, additional I_{Kr} blockade, considerable action potential and QT-interval prolongation ensue [5]. Cardiac myocytes thus express a broad range of ion channels with discrete voltage- and time-dependant properties which govern myocardial depolarization and repolarization. Alterations in the properties of these ionic currents can cause electrical disruptions which may lead to arrhythmias.

Correlations between the QT interval and arrhythmia risk date back to early descriptions of rare, inherited arrhythmia syndromes such as Romano-Ward Syndrome and Jervell and Lange-Neilsen Syndrome [6,7]. These two conditions now belong to the larger collective known as the Long QT Syndrome (LQTS). LQTS describes a collection of congenital and drug-induced arrhythmia syndrome subtypes that are characterized by a prolonged QT interval and a considerable risk of developing lethal cardiac arrhythmias. Gender is an important determining factor of the QT interval and associated arrhythmogenesis: QT intervals exceeding 460 ms for females and 440 ms for males are considered to be abnormally prolonged [8]. Landmark studies in the mid-1990s identified the molecular correlates of several congenital LQTS subtypes [9,10]. To date, up to ten different forms of congenital LQTS have been described; however, alterations in repolarizing K^+ currents form the basis of the mainstay of congenital LQTS [11].

The first association between a drug and the development of an arrhythmia probably dates back to the 1920s with the description

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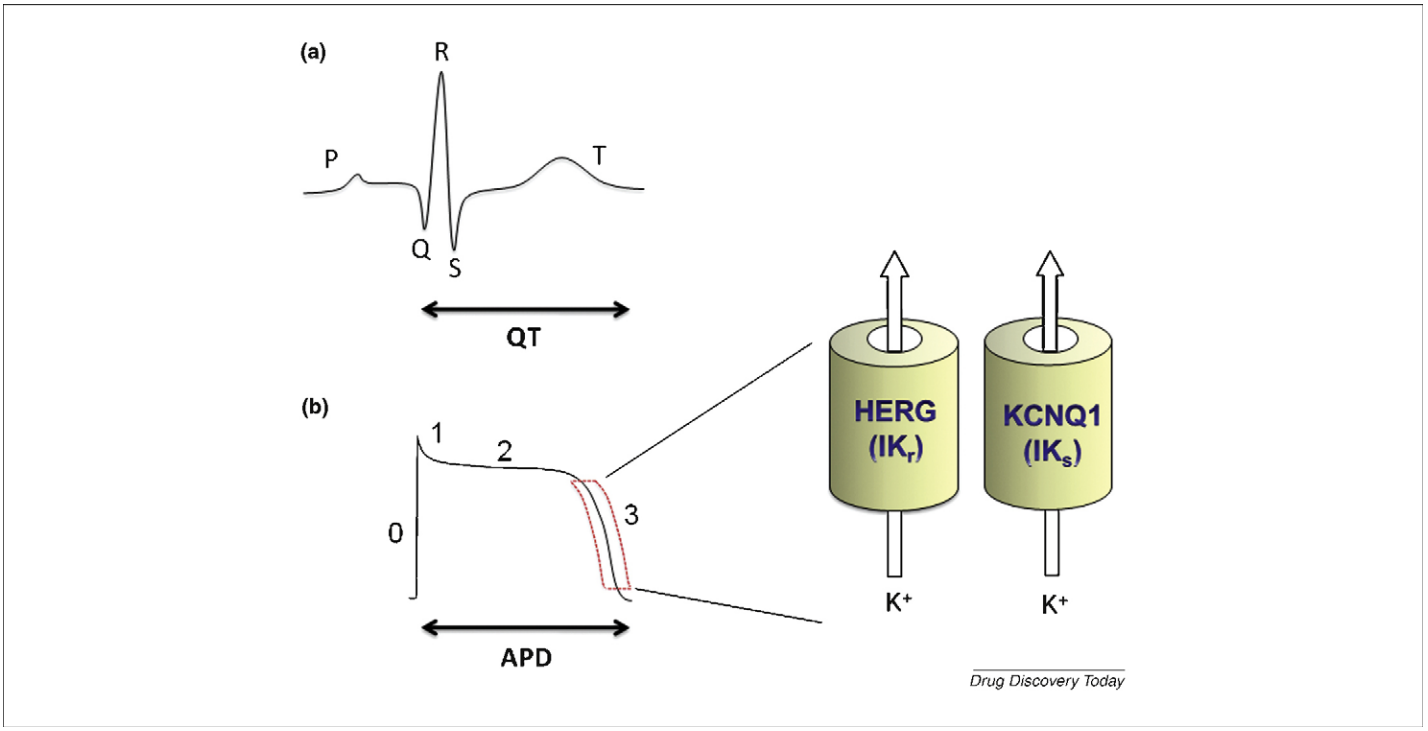

FIGURE 1

(a) The electrocardiogram (ECG) represents atrial depolarization (P wave), ventricular depolarization (QRS complex) and ventricular repolarization (T wave). The QT interval therefore is a measure of the time taken for the heart to return to a resting state following contraction of the ventricles. **(b)** The ventricular cardiac action potential represents Na^+ influx (ventricular depolarization, phase 0), transient K^+ efflux (phase 1), Ca^{2+} influx mediating excitation–contraction coupling (phase 2) and terminal repolarization through K^+ efflux (ventricular repolarization, phase 3), respectively. The two K^+ currents regulating phase 3 repolarization are the rapid and slow delayed rectifier currents (I_{Kr}, encoded by the HERG gene and I_{Ks}, encoded by the KCNQ1 gene, respectively). The QT interval of the ECG is a marker of ventricular action potential duration (APD).

of 'quinidine syncope' occurring with quinidine therapy [3]. It was not until much later, however, that an arrhythmia was identified as the cause of the syncope [12]. Shortly thereafter, Dessertenne coined the term '*torsade de pointes*' to describe an unusual arrhythmia where the QRS complexes appeared to 'twist around the isoelectric line' [13]. *Torsade de pointes* (TdP) is now among the most common arrhythmias encountered with cardiotoxic medications and is used exclusively to describe polymorphic arrhythmias occurring in the presence of a prolonged QT interval.

Within recent years, several medications have been removed from the market place owing to severe cardiotoxic profiles, including a prolongation of the QT interval and the development of TdP [3,14]. Ironically, more often than not, the chief culprits are antiarrhythmic medications such as dofetilide and ibutilide. Such drugs prolong the QT interval by as much as 50 ms when administered at therapeutic doses [3]. The risk of TdP is by no means a linear function of the QT interval, however, as some drugs have been removed from the market because of a high risk of TdP despite only modest QT interval increases of 5–10 ms [15].

Of particular cause for concern for the pharmaceutical industry is the increasing number of noncardiovascular drugs that induce QT prolongation or even TdP. Notable examples include terfenadine [16], cisapride [17], erythromycin [18] and fluoxetine [19]. Taking terfenadine as an example, between 1985 and 1996, 429 serious cardiac events were reported, 98 of which were fatalities. Initially attributed to cases of overdose, findings later emerged detailing cardiotoxicity associated with concomitant ketoconazole therapy [14]. Taken in the presence of ketoconazole, terfenadine induced large QT interval increases and posed a significant risk of arrhythmogenesis [20]. Basic pharmacological principles dictate that drugs possessing a single route of elimination are vulnerable to accumulation if that route becomes compromised, particularly through the use of other medications. In the case of terfenadine and ketoconazole cotherapy, saturation of hepatic cytochrome P-450 enzymes (CYP3A4) by ketoconazole prevented the otherwise rapid first pass metabolism of terfenadine, significantly elevating its plasma concentration and in turn causing a higher degree of QT prolongation [20] (Fig. 2). Similar pharmacokinetic–pharmacodynamic interactions leading to drug-induced arrhythmogenesis have also been linked to clarithromycin and disopyramide cotherapy [21]. The ability of drugs to induce QT prolongation and cause sudden cardiac death reflects a range of mechanisms taking place at the molecular, cellular, tissue and whole organ levels. Work conducted in the past 50 years has greatly increased our understanding of arrhythmogenesis.

Mechanisms of drug-induced arrhythmias: from cell to bedside

The majority of drugs that prolong the QT interval and predispose individuals to lethal arrhythmias do so through impairing repolarization, which at the cellular level often involves blockade of the human *ether-à-go-go* related gene K^+ channel (HERG) and a subsequent reduction in repolarizing I_{Kr}. Class III antiarrhythmic drugs, in particular the methanesulfonanilides group comprising dofetilide and the experimental compound E-4031 are potent blockers of the HERG K^+ channel [22,23]. Over the past decade

pharmacological inhibition of HERG K^+ channels has been associated with an increased risk for the development of cardiac arrhythmias leading to SCD. For instance TdP has been reported in up to 1–5% of patients receiving dofetilide treatment [24]. As a result of this there has been a reduced interest in the use of HERG K^+ channel inhibitors in antiarrhythmic therapy.

The methanesulfonanilides are thought to gain access to the channel pore upon depolarization and bind to a site near the selectivity filter. However, once inside the channel, these drugs become trapped when the activation gate of the channel closes during repolarization [25]. HERG K^+ channels have two key structural features that are considered to underlie the channel's ability to be blocked by an array of drugs that vary in both structure and size. Firstly, HERG K^+ channels lack the PXP motif usually found in the S6 helix of Kv1–Kv4 channels. Ordinarily this sequence acts to reduce the size of the channel's inner cavity, thus preventing the trapping of larger compounds inside the channel. Secondly, the presence of aromatic residues within the S6 helix (Y652 and F656) are believed to interact with the aromatic moieties of many drugs, acting in a manner to facilitate drug binding [26]. Furthermore, mutation of these residues significantly reduces HERG K^+ channel inhibition [27].

The density of ionic currents, particularly repolarizing K^+ channels, varies significantly throughout the heart. The resulting electrical heterogeneity within the myocardium results in APs that vary significantly in shape and duration in different regions [28–30]. This is particularly true in the left ventricle where differences (dispersions) in APD are encountered between the apex and base (apico-basal dispersions) [31] and even within the thickness of the ventricular wall itself (transmural dispersions) [32]. In the past decade, several studies have demonstrated that QT prolonging drugs amplify the transmural dispersion of repolarization, which can provide a necessary substrate for lethal arrhythmias [33].

At least three different cell types are thought to exist throughout the thickness of the left ventricular free wall: endocardial, midmyocardial (also known as the M-cell) and epicardial, in which repolarization times are longest in the M-cell layer [34,35] (Fig. 3a). Reduced expression of I_{Ks} in the M-cell layer, and hence, reduced repolarization reserve, partly underlies its longer repolarizing times and exquisite sensitivity to I_{Kr} blockade [36,37]. In the presence of an I_{Kr} blocking drug, disproportionate lengthening of the M-cell layer APD ensues, which in turn creates a zone of refractory tissue around which premature impulses circumvent and form re-entrant circuits – a common arrhythmogenic mechanism of action (Fig. 3b) [38]. It is now widely acknowledged that drug-induced TdP requires both a substrate and trigger. While alterations in the transmural dispersion of repolarization provide the substrate, premature impulses, arising from afterdepolarizations, act as the trigger [39].

Afterdepolarizations are fluctuations in the membrane potential occurring in the, otherwise smooth, repolarization phase of the cardiac action potential. On the basis of the time in which they arise in the action potential, they are defined as early (phase 3) or delayed (after full repolarization has taken place, phase 4) afterdepolarizations (EADs and DADs, respectively). If the amplitude of afterdepolarizations is sufficiently high, they can give rise to premature impulses (triggered beats) which perpetuate around zones of refractory tissue forming re-entrant circuits (Fig. 3b) [38]. Risk factors for EADs are remarkably similar to those which drastically increase the risk of arrhythmias in the presence of QT prolonging drugs: both bradycardia and hypokalemia significantly increase the incidence of EADs [40,41]. Such correlations

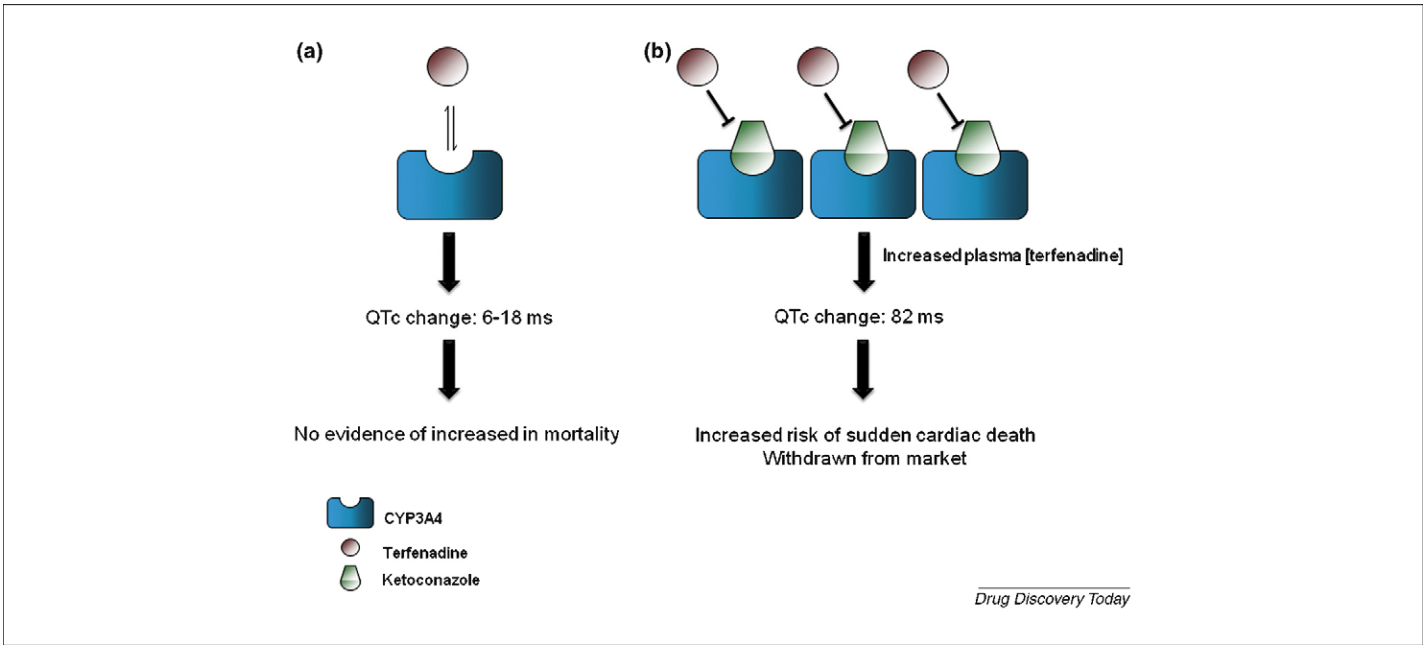

FIGURE 2

(a) Terfenadine therapy alone produced only small increases in the QT interval. **(b)** Taken in conjunction with ketoconazole, however, terfenadine produced large increases in the QT interval and cases of sudden cardiac death emerged, findings which eventually led to its withdrawal from the market. Ketoconazole saturated the pathway ordinarily responsible for terfenadine metabolism (CYP3A4 hepatic enzyme), elevating the plasma concentration of terfenadine, which subsequently produced a higher degree of I_{Kr} blockade and QT prolongation.

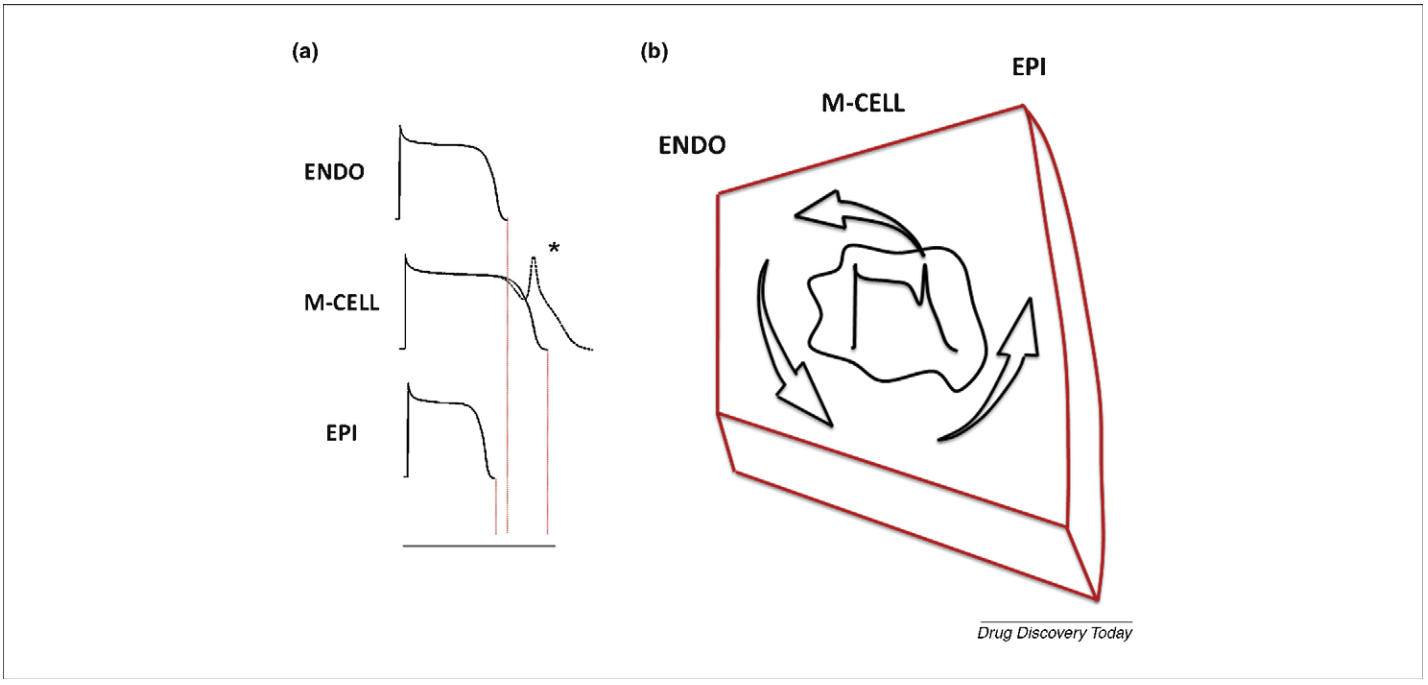

FIGURE 3

(a) Action potential durations (APDs) in the three cell types within the thickness of the left ventricular wall display marked heterogeneity, with the M-cell layer APD exceeding epicardial and endocardial APDs. Exposure to drugs that prolong the QT interval causes preferential prolongation of the M-cell APD, increasing the transmural dispersion of repolarization and causing EAD-induced triggered beats. **(b)** A proposed mechanistic framework for drug-induced arrhythmogenesis. Within the thickness of the left ventricular free wall excessively prolonged M-cell APDs generate EADs and triggered beats which can act as an arrhythmogenic trigger. Furthermore, pathologically prolonged M-cell action potentials in the midmyocardial zone of the left ventricle establish large zones of refractory tissue, indicating a close relationship between APD and the refractory period. Premature impulses, whether originating from the M-cell zone or from an external stimulus, are forced to circumvent these large zones of refractory tissue in a circular fashion as they propagate throughout the ventricular wall. Upon reaching their point of origin, the M-cell zone has recovered from refractoriness and is once again excitable and thus vulnerable to re-excitation by the circulating premature impulse. If re-excitation of the M-cell zone takes place, the zone of refractory tissue, and hence the arrhythmogenic obstacle, is once again established which creates a re-entrant arrhythmogenic circuit.

substantiate the role of EADs in triggering potentially life-threatening arrhythmias in the setting of QT prolonging agents.

Drugs prolonging the QT interval are a common cause of EADs [33,42]. Agents blocking I_{Kr} can significantly increase the APD in certain cell types in which the time spent in the window range of voltages for the L-type Ca^{2+} channel is increased so that it can recover from inactivation and open for a second time [43,44]. This pathological second influx of Ca^{2+} ions leads to a transient increase in membrane potential, the EAD, and may even give rise to salvos of triggered beats (Fig. 3a,b). A great deal of work has investigated the origin of EADs and reports have shown that they can, in fact, occur in most cell types if provoked [29,45,46]. Reports complimenting studies of transmural dispersion of repolarization, however, have suggested that EADs preferentially arise in the M-cell zone of tissue [46,47]. With this in mind, the M-cell layer can be considered to provide both the substrate and the trigger for lethal arrhythmias encountered with QT prolonging drugs. Partly in response to our increased understanding of how QT prolonging drugs can induce fatal arrhythmias, several preclinical assays now exist that aim to detect a potential arrhythmogenic signal of new chemical entities (NCEs).

Current methods to predict QT prolongation and arrhythmogenesis

Sudden cardiac death encountered with terfenadine and other drugs prompted the introduction of detailed preclinical cardiac safety assays by several regulatory bodies [14]. In 1997, the European Agency for the Evaluation of Medicinal Products outlined several preclinical assays for quantifying the risk of cardiac arrhythmias by NCEs [48]. This was followed by joint-initiatives from Health Canada and the Federal Drug Administration which detailed preclinical assays to be used when assessing arrhythmic liability of NCEs [14].

Clear evidence points to I_{Kr} inhibition in underlying QT prolongation and the formation of an arrhythomgenic substrate and triggers as the common mode of action of the majority of drugs implicated in TdP and sudden cardiac death [23,33,49]. Presently, a widely used preclinical screening strategy assesses, via single-cell electrophysiology, the ability of NCEs to reduce I_{Kr}. Whereas this approach may very well detect potent blockers of I_{Kr}, detailed studies of the effects on other ionic currents are also important. Potent L-type Ca^{2+} channel inhibition by verapamil, for example, probably offsets its I_{Kr} blocking abilities and TdP risk by shortening the APD [5]. Likewise, the multichannel blocking effects of amiodarone probably contribute to its low arrhythmia incidence, despite its ability to prolong the QT interval. With this in mind, testing the effects of NCEs on other ionic currents could help to ensure that potentially therapeutic compounds that may reduce I_{Kr}, but are not arrhythmogenic, are not lost at an early stage of drug development.

In addition to alterations in the QT interval and the dispersion of repolarization, other novel biomarkers of drug-induced sudden

cardiac death are extremely sensitive in predicting arrhythmogenesis. Firstly, notable beat-to-beat variations in left ventricular repolarization times have been reported following the administration of a potent HERG-blocking agent [50]. Thomsen *et al*. [50] investigated the risk of arrhythmias in an *in vivo*, anaesthetized canine model subjected to acute atrioventricular block. Exposure to dofetilide induced a transient increase in the short-term variability (STV) of left ventricular repolarization times only in proarrhythmic animals; animals exhibiting no increases in STV in response to dofetilide did not develop arrhythmias [50]. Such findings clearly point to measurements of STV as a potentially powerful tool for risk stratification in patients undergoing therapy with HERG-blocking drugs.

Secondly, monitoring changes in the shape of the action potential, beyond duration, in response to drugs delaying repolarization has gained considerable popularity as an arrhythmogenic predictive tool. Measuring changes in a range of action potential characteristics is likely to yield a more sophisticated analysis of the arrhythmic liability of drugs. Action potential triangulation is determined by measuring the duration of phase 3 repolarization and increases in triangulation have been associated with a high risk of arrhythmogenesis [51]. It is now common to combine measurements of triangulation with those of reverse-rate dependence, temporal APD instability and dispersion of repolarization (an analysis known as TRIaD) to accurately determine the risk of drug-induced arrhythmogenesis [52,53].

The application of pharmacogenetics to the study of drug-induced arrhythmias and sudden cardiac death has the potential to shed important light on the mechanisms of adverse cardiac drug effects at the genetic level. It is now recognized that a single drug can invoke a range of responses in patients, and this is particularly true in the context of drug-induced arrhythmias. Our understanding of the potential clinical effects of subtle, subclinical, lesions in cardiac ionic currents in response to drugs that delay repolarization has been significantly advanced by the use of mathematical models. Clancy *et al*. [54], for example, used a computational model of genetically altered Na^+ channels to predict the cellular effects (including changes in APD) of common antiarrhythmic medications in patients carrying these mutations [54].

Alternative mechanisms of drug-induced arrhythmogenesis, beyond blocking of the HERG K^+ channel, are emerging and, as such, modifications in drug screening strategies must be implemented to accommodate this new information. Downregulation of the HERG channel protein following exposure to I_{Kr} blockers has now been demonstrated for several drugs which prolong the QT interval [55]. An increase in inward I_{Na} likewise impairs repolarization [56,57] and has been reported to underlie QT prolongation with the antiarrhythmic agent ibutilide [58].

Risk stratification of drugs by ionic current measurements alone is certainly a reductionist's approach to understanding arrhythmogenic mechanisms and predicting TdP. Arrhythmias are, by their nature, complex, multicellular events and using findings from the single-cell level to predict events at the whole heart level must be done with extreme caution. Accordingly regulatory bodies have implemented the use of several *in vitro* (Purkinje fiber and canine ventricular wedge preparations) alongside *ex vivo* (Langendorff-perfused rabbit heart model, for example) and *in vivo* (telemetry recordings in rabbits, for example) experimental systems. These models have shed important light on arrhythmogenic mechanisms in the setting of drugs that prolong the QT interval and have been extensively reviewed elsewhere [14]. Limitations exist, however, regarding the translatability of these experimental models. Isolated tissue preparations are devoid of electrotonic coupling seen in the intact heart which can have important impacts on arrhythmogenesis [59]. Additionally, species-dependant variability of cardiovascular electrophysiology can complicate the transfer of findings from the laboratory to the clinic. A low level of repolarization reserve in the rabbit heart, for instance, appears to underlie its high sensitivity to EADs and arrhythmias in the presence of HERG-blocking drugs [60].

Despite the limitations of current cardiac safety screening procedures, the industry is actively engaged in the crucial assessment and development of preclinical cardiac screening technologies. Recently, the International Life Sciences Institute's Proarrhythmic Models Project Committee held a workshop to address the relationship between drug effects on ventricular repolarization and the clinical event of TdP. The molecular and cellular basis for TdP, the dynamics of periodicity and models of TdP proarrhythmia were among the areas highlighted in which further research could yield significant advances in our ability to detect proarrhythmic drugs early in development (for a review, please see [48]. Furthermore, several emerging technologies have made possible significant advances in predicting drug-induced arrhythmias and, as such, may have an important impact upon how the pharmaceutical industry profiles the cardiac safety of NCEs.

Emerging technologies in preclinical cardiotoxicity screening

Zebrafish

The zebrafish has emerged as a powerful tool for not only the developmental biologist, but also the cardiac electrophysiologist [61–63]. The zebrafish heart begins to beat as soon as 24 hours after fertilization and, in the two to three days that follow, it develops from a primitive tube to a two-chambered vessel, complete with a thickened ventricular wall, repolarization heterogeneity and intrinsic myocardial pacemakers [64].

Important observations have shown striking similarities between zebrafish and human cardiac electrophysiology. Ventricular APs recorded from the zebrafish heart are of a similar shape and duration to human APs [65] and contain a substantial amount of repolarizing I_{Kr} [66]. Furthermore, QT prolonging drugs induce bradycardia in embryonic zebrafish (in keeping with episodic bradycardias seen in HERG-deficient, LQT2 patients) and even produce a long QT interval in adult fish [67]. The studies of heart rate changes in embryonic fish in response to pharmacological agents can even be conducted at a high-throughput rate, increasing the attractiveness of this assay for the pharmaceutical industry. Embryonic zebrafish can be distributed in 96-well plates (more than one fish can be placed in each well) and an automated plate reader can record the heart rates of each fish in all 96 wells within approximately 10 min (personal observation). Embryonic fish are placed in wells containing either a control solution or a test compound. In keeping with traditional high-throughput cell-based screening technologies in the pharmaceutical industry, the effects of several different compounds at a range of concentrations can be measured in one 96-well plate using this assay. QT-interval measurements in adult zebrafish are, however, more labor intensive.

Although measurements of increased QT interval may not necessarily correlate to an increased risk of arrhythmia, it remains possible that more sophisticated analyses, such as those incorporated in TRIaD studies, can be adapted for use in the zebrafish heart. The finding of bradycardia in embryonic zebrafish in response to drugs that are known to prolong the QT interval in humans could potentially have important implications for the study of drug-induced LQTS in pediatric patients. Lewin *et al.* [68] reported that cisapride induced not only QT-interval prolongation in a two-month-old infant but also 2:1 atrioventricular (AV) block; findings identical to those seen in embryonic zebrafish hearts [67,68]. Such findings point to the utility of this model system for also detecting adverse cardiac events associated with drug-induced LQTS in pediatric patient populations.

Genetic manipulation in the zebrafish can also be done with relative ease, even postfertilization [67]. The injection of morpholinos at the single-cell stage can selectively suppress gene transcription and therefore protein translation [69]. Such maneuvres make possible the study of cardiac repolarization and arrhythmia susceptibility in the background of genetically altered subclinical lesions in ion channel function: clinically relevant conditions in keeping with recent advancements in our understanding of repolarization reserve [70].

Although the zebrafish heart exhibits action potentials bearing close resemblance to those recorded from the rabbit, canine and even the human heart, and manifests electrocardiographic QT prolongation in response to drugs that reduce I_{Kr}, it remains to be seen whether rapid ventricular arrhythmias can be generated and sustained in the zebrafish heart. Nevertheless, low maintenance costs coupled with important physiological similarities are enabling zebrafish to gain considerable popularity in the pharmaceutical industry not only for toxicology screening, but also in target identification and lead discovery [69].

Stem cells

Several studies have demonstrated the feasibility of using stem cells to help predict drug-induced arrhythmogenesis [71,72]. Cardiac myocytes cultured from human embryonic stem cells display intrinsic electrical activity which is sensitive to pharmacological perturbation and extracellular field potential recordings can provide noninvasive measurements of repolarization with waveforms resembling ECG recordings [72]. It is important to note, however, that although morphologically similar to ECG recordings, the physiological basis of field potential recordings in populations of myocytes is extremely different to that of the ECG and as such the interpretation of such recordings must be done with great care. The nature of these assays – electrotonically coupled ventricular myocytes containing a full complement of ionic channels – permits them to yield a considerable amount of physiologically-relevant information, a distinct advantage to recording isolated ionic currents in mammalian expression systems. One of the main limitations concerning the use of stem cell derived cardiac myocytes in predictive cardiotoxicity, however, is the inability to culture ventricular myocytes possessing the properties of electrophysiologically distinct cells (epicardial, endocardial or M-cell). Despite this, however, the ability to screen NCEs in cultured ventricular myocytes circumvents the extremely labor-intensive process of enzymatically dissociating single myocytes from perfused whole hearts. Therefore the ability to culture high numbers of myocytes at any given time has the potential to remove important rate-limiting factors in preclinical cardiotoxicity screening such as the high cost of enzymes to isolate native myocytes and the long periods of time that this process ordinarily takes.

Each assay, whether current or emerging, has distinct advantages and disadvantages for predicting cardiotoxicity. While being a relatively high-throughput assay, automated patch clamp HERG K^+ current recordings from heterologous cell lines are limited in their translatability. Conversely, whole heart and *in vivo* preparations possess a higher degree of translatability, but are extremely low throughput. Fig. 4a scores existing assays and emerging technologies in terms of translatability and throughput in an attempt to visualize the strengths and weaknesses of each platform.

The four forces shaping preclinical cardiotoxicity

The challenging and dynamic nature of preclinical cardiac assessment is thus determined by four forces (Fig. 4b). Each force carries a considerable amount of power in shaping the state of preclinical cardiac safety screening in the pharmaceutical industry.

Translatability

Translatability remains at the forefront of the pharmaceutical industry's mind. Questions remain regarding the utility of existing cellular, tissue and *in vivo* preparations in predicting adverse cardiac events in larger patient populations. The ability of a NCE to block I_{Kr} at the single-cell level, for example, does not always translate to an increased risk of sudden cardiac death.

Unknown arrhythmogenic modes of action

Unknown and novel arrhythmogenic modes of action of QT prolonging drugs are challenging the validity of current approaches to predict cardiotoxicity. By focusing efforts predominantly on searching for an I_{Kr}-antagonist arrhythmogenic mode of action, the pharmaceutical industry is potentially exposing itself to cardiotoxicity induced by other mechanisms, such as HERG downregulation and increases in inward currents.

Regulatory bodies

Increasingly stringent regulatory requirements now demand testing of NCEs at the ion channel and *in vivo* levels. If a potential QT prolonging signal is detected in these assays, further studies are required to demonstrate safety. As history has shown thus far, the nature of tests required by regulatory bodies is likely to evolve as new findings, which increase our understanding of drug-induced arrhythmias, emerge. Rapid incorporation of such findings and subsequent changes to testing procedures, if necessary, are vital to minimize the effects of information asymmetry between the basic research and drug discovery communities.

Emerging technologies

Emerging technologies offer new opportunities to improve throughput, lower the cost or increase the translatability of existing preclinical cardiac safety assays. As such, they can challenge the validity of currently used methods. Adoption of new technologies, however, must only take place following a complete understanding of both their advantages and limitations.

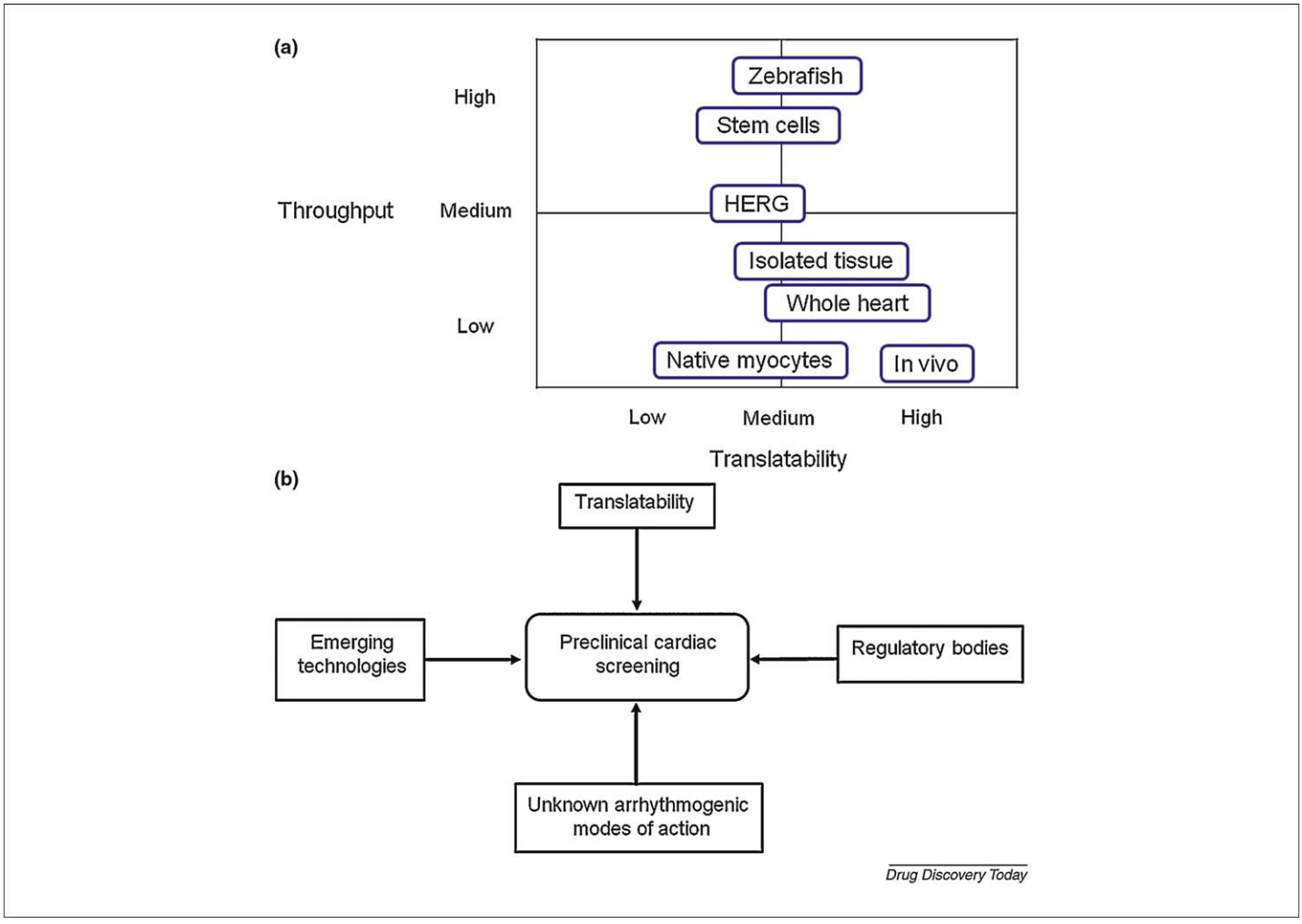

FIGURE 4

(a) Scoring current and emerging cardiac safety screening technologies in terms of translatability and throughput reveals their respective strengths and weaknesses. **(b)** Four forces currently shape preclinical cardiac safety screening: translatability, unknown arrhythmogenic mechanisms of action, regulatory bodies and emerging technologies.

Summary

Sudden cardiac death is a leading cause of mortality in the developed world and as such it represents a considerable public health burden. An increasing number of medications for a wide range of conditions, from arrhythmia to allergy, infection and depression, are capable of prolonging the QT interval and potentially causing fatal arrhythmias. Crucial interaction between a substrate (an altered dispersion of repolarization) and a trigger (an EAD-induced triggered beat) is thought to underlie drug-induced arrhythmogenesis. Accordingly, regulatory bodies have highlighted a number of preclinical safety assays to detect arrhythmogenic signals of NCEs including I_{Kr} screening in mammalian cell lines, isolated cardiac tissue recordings and QT-interval measurements at the whole heart level [14]. These assays, however, have limitations which can dramatically affect the translatability of findings. The recognition of additional mechanisms by which drugs can prolong the QT interval and induce fatal arrhythmias must be addressed to ensure the continued safety of licensed medications. New experimental platforms, such as the zebrafish, are emerging which have potential to benefit preclinical cardiotoxicity assessment. The four forces at play in shaping preclinical cardiac safety screening (translatability, unknown arrhythmogenic modes of action, regulatory bodies and emerging technologies) therefore contribute to its dynamic nature. Strategies to improve the level of preclinical cardiac safety in drug discovery thus demand a fundamental understanding of these forces.

Importantly, the perceived risk of any drug must be weighed against the potential clinical benefits that it could offer patients. In terms of chronic, terminal or debilitating illnesses where there is a paucity of effective medications, new treatments that offer significant improvements in these medical conditions but which also cause mild QT prolongation would be viewed much more favorably by regulatory bodies than, for example, a new allergy medication that prolongs the QT interval to a similar extent. A thorough analysis of a new drug's risk/benefit ratio is one of the most important factors that could influence its ultimate approval. This is especially true in crowded markets where a plethora of alternative treatments could exist that have better safety profiles.

Conflicts of interest

The author reports no conflicts of interest.

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