scheme in their new Class 0, and the late sodium current blocker and potential treatment for the pro-arrhythmic long QT3 syndrome, ranolazine, appears in an expanded Class Id.

The original Class II group of autonomic nervous system inhibitors and activators beyond the selective (IIa) and non-selective (IIb) beta-adrenergic inhibitors to include muscarinic receptor inhibitors (IIc) and activators (IId) and adenosine receptor activators (IIe).

The group of potassium channel inhibitors and openers (Class III) is expanded from the original non-selective potassium channel blockers (such as amiodarone) to include subsequently discovered selective IKr (dofetilide), possible IKs, IKur (vernakalant), Ito (tedisamil), IKATP (nicorandil), and IKAch (BMS914392) specific drugs.

The more extensive new Class IV now incorporates major recent advances in understanding of cellular calcium homeostasis. Thus, to the original cell surface membrane calcium channel blockers (IVa), are added blockers of intracellular calcium channels (IVb), and agents targeting active sarcoplasmic reticular calcium transport (IVc), membrane ion exchangers (IVd), and enzymes affecting phosphorylation of biologically important proteins (IVe) for which there are currently no clinically approved drugs, for the first time.

Prof. Lei said: 'We also tackled the problem of multiple drug targets, rationalized adverse, even pro-arrhythmic, actions shown by particular drugs under particular arrhythmic circumstances, pointing out new strategies/directions for new anti-arrhythmic drug development'.

This article, say the authors, thereby successfully developed an expanded, yet pragmatic classification of both clinically approved and potential arrhythmic drugs. 'This updates the original Vaughan Williams/Bramah Singh approach, capturing advances in cardiac physiology and pharmacology in the 50 years following its original publication. Previous attempts at updating this initial classification had achieved only limited success', said Lei.

Prof. Huang, who is Professor of Cell Physiology in the University of Cambridge, suggested: 'The paper will provide an updated guide to basic understanding of the principal and subsidiary categories of antiarrhythmic and proarrhythmic drug actions in terms of their electrophysiological actions on specific currently known and potential targets bearing on cardiac excitation. It remedies the current conceptual mismatches between basic research insights and outcomes of new antiarrhythmic therapeutic strategies and drugs'.

The authors raised serious concerns about the implications of this mismatch.

Prof. Lei continued: 'This mismatch had resulted in a situation that has impaired both clinical management and progress in the field of cardiac arrhythmia and its management, which has lagged behind therapeutic advances in other clinical areas. There are even situation in which antiarrhythmic drugs actually worsen arrhythmia death rates. Furthermore, negative, pro-arrhythmic, drug effects have hindered development of numerous new drugs for the full range of remaining human diseases. All this has led to a loss of confidence in both existing and potential future antiarrhythmic drugs by both clinicians and pharmaceutical companies'.

Both authors hope their paper on Modernized Classification of Cardiac Antiarrhythmic Drugs will prompt the establishment of new high-level formal strategic guidelines for clinical selection of specific drugs and related treatment strategies for current clinical management based on basic scientific insights appropriate to the present day, facilitating therapeutic decisions in current clinical practice.

It will, they suggest, encourage rational clinical use of existing available anti-arrhythmic drugs in relationship to their particular mechanisms of action, thus optimizing treatment decisions, and prompting new strategies for current clinical practice. They also hope it will promote the discovery of future drugs and therapies for managing cardiac arrhythmias, improving clinical practice; and facilitating the development of new antiarrhythmic drugs.

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Reference

1. Lei M, Wu L, Terrar DA, Huang CL-H. Modernized classification of antiarrhythmic drugs. *Circulation* 2018;**138**:1879–1896.

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Late onset heart failure after childhood chemotherapy

Improved oncology treatment has dramatically increased the number of long-term cancer survivors, but the potential cardiovascular side effects from the cancer treatment are increasing their morbidity and premature mortality.[1] This is particularly true for paediatric cancers patients who are commonly treated with anthracycline chemotherapy (AC) and/or radiotherapy to the chest (RT), because the developing children's heart appears more sensitive to the cardiotoxic effects.[2,3] Acute (early-onset) AC-induced cardiotoxicity (AIC) interferes with optimal cancer treatment if interruptions or changes to cancer treatment are required.

However, for paediatric cancer survivors the major clinical problem is cardiovascular disease years after treatment [late-onset cardiotoxicity (LOC)]. Second malignancies are also more common in paediatric cancer survivors, further increasing the risk for additional cardiotoxic cancer therapies in patients with prior cardiac injury.[4] Late heart failure following anthracyclines is particularly treatment-resistant and is associated with a poor prognosis. Therefore, recent guidelines recommend lifelong follow-up of paediatric cancer survivors and especially of those at risk for cardiovascular toxicity.[5]

Currently, the clinical approach is to treat heart failure after it has presented. However, if we can develop an improved understanding of the molecular pathophysiology then the opportunity to treat and prevent heart failure in cancer survivors becomes a new option. In this regard, toxic mitochondria iron accumulation is induced by AC in

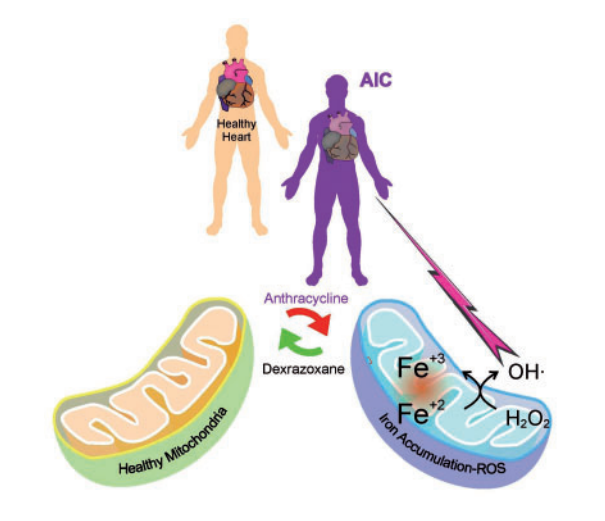

Figure 1 Mitochondria with and without Iron.

cardiomyocytes and dexrazoxane has been shown to protect cardiomyocytes from doxorubicin induced toxicity (*Figure 1*).[6] Dexrazoxane has recently been approved for use in paediatric patients[7] and a recent systematic review in paediatric cancer survivors treated with anthracyclines suggests that administration of dexrazoxane may also reduce LOC.[8]

The dose of AC and/or RT, the patient's age and cancer type, treatment duration, and disease relapse are risk factors for LOC.[8] There is no proven diagnostic test to identify patients with higher risk LOC prior its clinical manifestation, although emerging data suggests reduction in global longitudinal strain on speckle echocardiography in paediatric cancer survivors may precede heart failure presentation. Furthermore, also knowledge on additional 'second hit' risk factors that may trigger clinical manifestation of LOC.

In addition to the risk associated with the growing heart in children, genetic risk factors may play an important role. These include cardiomyopathy-related genes or therapy-induced changes in metabolic pathways leading to prolonged and/or higher serum concentrations of toxic chemotherapeutic substances. Genome-wide association studies have shown variants in the *retinoic acid receptor gamma* (*rarg*), *cugbp elav-like family member 4* (*celf4*) as possible genetic factors predisposing to cardiac damage following anthracycline therapy.[9,10] Several other studies have focused on the identification of genetic predictors using a candidate gene-based approach[11] showing for example that polymorphism in the *carbonyl reductase* genes (*cbr3*)[12] and (*cbr4*),[3] *electron transfer flavoprotein beta subunit* (*etfb*),[13] *G protein-coupled receptor 35* (*gpr35*),[14] and *hyaluronan synthase 3* (*has3*)[3] may influence genetic predisposition for LOC in paediatric cancer survivors.

Recent work has demonstrated that human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CM) accurately recapitulate a patient's predisposition to AIC.[15] This exciting finding confirms that AIC has a genomic basis and that hiPSC-CM can be used for elucidating the genetic variants responsible. In addition, genetic predisposition to tumour disease may also impact on the risk for LOC. For example, the tumour suppressor *breast cancer1* (*brca1*), which is mutated in early onset familial breast and ovarian cancer and plays an important role in DNA repair mechanisms of the cardiomyocyte.[16] Mutations in such genes may on the one hand lead to cancer but may also affect the response of the cardiomyocyte to cardiotoxic treatment, as it may play a role in anti-tumour therapy induced damage and damage repair, thereby modulate the risk for LOC. It has also been demonstrated that erythropoietin may promote repair mechanisms in the heart, especially in cardiac progenitor cells,[17] thereby reduce the risk for LOC. Recent findings indicate that specific pathways including PI3Kγ, can be up-regulated in the heart after anthracycline therapy and may contribute to heart failure development which not only involve cardiomyocytes but also inflammatory cells (leucocytes), thus potentially providing a new strategy to develop biomarkers for AIC and LOC risks.[18]

Lifestyle measures are also important factors determining the risk for late onset cardiotoxicity. For example, exercise is beneficial in cancer patients during and after chemotherapy and may reduce the risk for LOC.[19] This is particularly important as childhood cancer survivors are less physically active than the general population and adult survivors are more likely to report a sedentary lifestyle than their siblings.[20] In addition, future cardiovascular stress insults may trigger cardiovascular disease at a lower threshold in patients previously treated with cardiotoxic chemotherapy or RT.

One common and important issue specifically for female paediatric cancer survivors, especially with the advances in oocyte preservation and reproductive science, is pregnancy. Pregnancy induces high mechanical and neurohormonal stress on the maternal cardiovascular system and needs complex signalling networks to prevent damage of the heart.[21] Impairment of these cardioprotective networks, which includes pathways typically targeted by anti-cancer treatment, such as Vascular Endothelial Growth Factor A (VEGFA), Signal Transducer And Activator Of Transcription 3 (STAT3), or Neuregulin-1 (Nrg1) signalling, lead to peripartum cardiomyopathy.[22] Indeed, there is accumulating evidence that anti-cancer treatment could predispose women for peripartum heart failure later in life.[23,24]

The appearance of AIC and LOC in cancer survivors together with the complexity of acute cardiovascular toxicity from many novel cancer therapies has led to the development of cardio-oncology as a new medical subspecialty, with specialist cardio-oncology centres created to address this growing medical problem.[25] New strategies to detect toxicity earlier with sensitive cardiac biomarkers and imaging are being implemented.[26] However, to date the molecular mechanisms of late onset cardiotoxicity are incompletely understood and no biomarkers are available for monitoring and prediction for LOC disease risk and no approved specific co-treatments to prevent LOC are available. Exploring both the mechanisms of acute and long-term cardiovascular side effects of anti-tumour therapies, to develop early markers and preventive and curative treatment is needed not only to reduce cancer disease but to improve morbidity and mortality of cancer survivors.

We believe this can be achieved by combined interdisciplinary efforts of clinicians and scientist from oncology and cardiology working together in cardio-oncology science.

Denise Hilfiker-Kleiner[1], Hossein Ardehali[2], Rodolphe Fischmeister[3], Paul Burridge[2], Emilio Hirsch[4] and Alexander R. Lyon[5,6]

[1]Department of Cardiology and Angiology, Medical School Hannover, Germany; [2]Northwestern University Feinberg School of Medicine, Chicago, USA; [3]Inserm UMR-S 1180, Faculty of Pharmacy, Univ. Paris-

Sud, Université Paris-Saclay, Châtenay-Malabry, France; [4]Department of Molecular Biotechnology and Health Sciences, University of Torino, Italy; [5]Cardio-Oncology Service, Royal Brompton Hospital, London, UK; and [6]National Heart and Lung Institute, Imperial College London, UK

Corresponding author:
Denise Hilfiker-Kleiner, PhD
Dept. of Cardiology and Angiology
Hannover Medical School
Carl-Neuberg Str. 1
30625 Hannover, Germany
Phone: +49-511-532-2531, Fax: +49-511-532-3263
Email: hilfiker.denise@mh-hannover.de

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References

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Tales in Cardiology

A revival for narrative medicine is taking place in Rome

I see no reason or need for my doctor to love me—nor would I expect him to suffer with me. I wouldn't demand a lot of my doctor's time: I just wish he would brood on my situation for perhaps five minutes, that he would give me his whole mind just once, be bonded with me for a brief space, survey my soul as well as my flesh, to get at my illness, for each man is ill in his own way.

Anatole Broyard, The patient examines the doctor.[1]

In an era of medicine marked by overwhelming technology and obsessive emphasis on Evidence-Based Medicine, the role of patients' narratives has progressively lost the key function of driving medical decisions, as it has been doing for centuries. While technology outweighs a physical examination by providing more detailed information, it cannot replace the information resulting from the storytelling of patients, caregivers, or other doctors, nor the physician–patient human interaction, which is important, often crucial, for successful treatment. The storytelling is pivotal in many cardiovascular conditions: heart failure (just think of NYHA functional classes) myocardial infarction or angina, syncope, and thromboembolism are paradigmatic examples. In all these conditions, the essential clinical steps are: 'To listen, to understand, to care'.

For these reasons, at the Cardiology Department of the School of Medicine of 'Sapienza' University, Sant'Andrea Hospital in Rome, we have developed a multidimensional program to enhance the role of narrative medicine in the education of medical students, young physicians, and cardiology residents, and, more so, for the management of heart failure patients.

Figure 1 Sant'Andrea—'Sapienza' University Hospital, Rome, Italy.

Narrative medicine in the third millennium

The main role of the medical profession is to cure patients and not diseases; to take care of every patient suffering from any illness as a whole and unique person, because, following Anatole Broyard, 'each man is ill in his own way'.

Figure 2 Massimo Volpe with the 'Narrative Cardiology' team at Sant'Andrea Hospital (L to R: Roberta Coluccia, MD, PhD; Massimo Volpe, MD; Andrea Laurito, MD student, experimental thesis in Narrative Cardiology; Livia Pescarollo, MD, Anaesthesiology Resident; and Marco Testa, MD, PhD, FESC, Cardiology Staff).