On the horizon in heart failure

Chronic heart failure is a dangerous, debilitating, and common disease, subjecting patients, carers, and doctors to a substantial burden. The need for admission to hospital and provision of specialist care, often for extended periods, means that the costs to health systems are correspondingly great. In the UK, some 1% of people have heart failure and, as of June, 2010, a stark 32% of people admitted with heart failure died within 1 year.

In Europe, about 14 million people are thought to have heart failure, and congestive heart failure affects an estimated 4·8 million Americans. In the developing world, the data are less certain. The World Heart Failure Society reports that no English-language epidemiological studies on heart failure are available from China, but incident cases of heart failure in India were estimated at 0·49–1·8 million in 2010. The ongoing demographic ageing of populations in the developed world, along with the inescapable transition to non-communicable disease in developing countries, mean that management of heart failure can only grow as a concern for patients, doctors, and health-system architects worldwide.

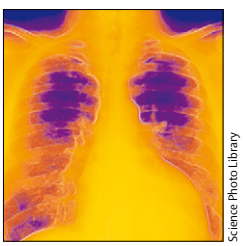
Many possible causes of heart failure exist, with ischaemic myocardial damage and valve dysfunction being major contributors at the population level. Infectious diseases, culminating in rheumatic heart disease for example, are important in some regions. Prevalence of heart failure is understandably raised in people older than 60 years and is exacerbated by poor control of hypertension, diabetes, and other risk components. Comorbidities can be expected to greatly complicate medical treatment and care, especially in elderly patients, and depression is common.

In today's *Lancet*, Ajay Shah and Douglas Mann review scientific advances in understanding of the cardiac remodelling underlying chronic heart failure with depressed left ventricular ejection fraction. In the past decade, knowledge about the relevant mechanisms, and especially molecules, involved has burgeoned as a result of basic research. However, the need to progress from attractive drug targets in cardiomyocytes, through translational model systems of limited fidelity, to decisive clinical trials of new drugs in chronically ill patients means that tangible returns on the investment in research have arguably been small—with ivabradine a possible exception.

Henry Krum and John Teerlink discuss treatment options in medical therapy for chronic heart failure with reduced or preserved ejection fraction. In recent decades, pharmacological treatments have evolved progressively to improve prognosis for patients with heart failure. Although a well honed sequence of treatments, consisting of diuretics, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, β blockers, and other agents is recognised in systolic chronic heart failure, the picture is less clear in heart failure with preserved ejection fraction. Krum and Teerlink also highlight new agents on the therapeutic horizon, and two accompanying Articles present promising research on omecamtiv mecarbil, a selective cardiac myosin activator that prolongs systole. This agent has reached the phase 2 stage of clinical development for treatment of systolic heart failure, and might provide an alternative to existing inotropic drugs.

Two further reviews consider nonpharmaceutical aspects of the treatment of patients with heart failure. Implantable cardioverter defibrillators are standard therapy for patients at risk of sudden cardiac death. Cardiac resynchronisation therapy with a pacemaker or defibrillator is another well established treatment, with beneficial effects on the underlying mechanisms of disease in appropriate groups of patients with heart failure. Telemedicine in management of heart failure is also addressed. The aspiration in telemedical approaches to heart failure is to monitor adherence to care plans to the benefit of medical outcomes and quality of life for patients, to optimise the use of scarce specialist expertise in cardiology, and to reduce admissions. Substantial practical limitations remain in development of safe and effective cardiotelecommunication systems, however.

A *Lancet* Editorial published in December, 2010, discussing England and Wales' third National Heart Failure Audit, concluded that "Currently the NHS spends up to £1 billion a year, apparently on managing heart failure badly". The next audit should allow progress in increasing coverage with beneficial drugs to be judged, along with possible improvements in organisation of heart failure care in the NHS (in times of considerable organisational turbulence). In the meantime, we look forward to further research on new interventions that can improve outcomes for patients with heart failure, and not only in rich countries. ■ *The Lancet*



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For the **2010 *Lancet* Editorial** see *Lancet* 2010, **376:** 2041

Doctors striking in Israel

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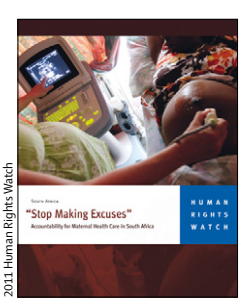
Starting on April 5, doctors in Israel have been taking part in a series of strikes in protest over the worsening conditions and staff shortages in public hospitals. Israel had 3·36 doctors per 1000 people in 2010, but this number is predicted to fall to 3·09 per 1000 by 2015 and 2·69 per 1000 by 2025. The strikes were a last resort after at least 8 months of unsuccessful negotiations with the Israeli Government. During the strikes, public hospitals have been intermittently operating on a Sabbath (ie, reduced) schedule. Even with doctors striking, negotiations between the Israeli Ministry of Finance (MoF), which plans and implements the government's economic policy, and the Israel Medical Association (IMA), an independent and apolitical organisation that represents physicians in Israel, have resulted in little progress.

IMA's requests for reforms of the health system include a 50% increase in the hourly wage for doctors in the public sector, as well as bonuses for those working in outlying, underserved areas where life expectancy is shorter and in understaffed specialties. They also seek improved working conditions, increases in the time allocation per patient from 10 min to 12–15 min, and an extra 1000 posts for doctors. Leonid Eidelman, chairman of the IMA and an anaesthetist, started his hunger strike on July 25 outside Benjamin Netanyahu's office to persuade the Prime Minister to intervene. On Aug 3, Eidelman ended his hunger strike after progress had been made in negotiations between the IMA and the MoF.

On Aug 14, the IMA decided to resume striking over disagreements that included medical staff having to clock in and out, and residents wanting the state hospitals to offer services that are covered by the supplemental insurance programmes of health maintenance organisations. Some residents and specialists have resigned because of the lack of progress and their resignations will go into effect in September. Although being continuously briefed about the negotiations, why is the Prime Minister, who is also the Minister of Health, seemingly reluctant to intervene and bring the strikes to a swift end? ■ *The Lancet*

South Africa should step up oversight of maternal care



2011 Human Rights Watch

If the moral test for a society is the way in which it treats its most vulnerable citizens, then the release of a new report by Human Rights Watch (HRW) marks a sad day for South Africa.

The report, *Stop Making Excuses: Accountability for Maternal Health Care in South Africa*, details the poor state of maternity care in South Africa, including the abuse of pregnant women by health workers. It makes for shocking reading. HRW interviewed more than 150 women who had sought health care in the Eastern Cape province and found that most women had experienced physical and verbal abuse in these settings. Some women had been pinched, slapped, or handled roughly during labour, pregnant women with HIV had been ridiculed, and migrant women had experienced xenophobia. Refugee women also told HRW that some staff withheld maternity services from them until bribes were paid. Women were also discharged too early, sent home without pain medication, and refused admission when in labour.

Disturbingly, the abuses uncovered by HRW are not new. As *The Lancet*'s 2009 Series on South Africa noted: "Reports and observations of rude and sometimes abusive behaviour by health workers, especially in the maternal setting, are widespread." Although there are factors underlying these attitudes such as poor pay and long working hours, as HRW states, the time for excuses is over. Such behaviour is unacceptable.

The HRW report notes that this abuse occurs because oversight and accountability mechanisms are not working in the country and calls for internal monitoring of policies, practices, and performances such as a facility-based complaints mechanism for patients and the establishment of a national office of a health Ombudsperson. These recommendations should be actioned without delay.

Health-care managers must take responsibility for what happens at facilities. They should monitor recruitment and training practices, implement mentoring and motivational strategies for staff, and ensure disciplinary action is taken against those found to be mistreating patients. South Africa can, and must, do more to help mothers. ■ *The Lancet*

For the **HRW report** see http://www.hrw.org/reports/2011/08/08/stop-making-excuses-0

For **2009 *Lancet* Series on South Africa** see http://www.thelancet.com/series/health-in-south-africa

Cardiac myosin activation: will theory and practice coincide?

See **Articles** pages 667 and 676

Albert Einstein wrote: "In theory, theory and practice are the same. But in practice, they are not." In *The Lancet*, two papers[1,2] investigate a novel cardiac myosin activator, omecamtiv mecarbil, a compound with inotropic action that is a potential therapeutic alternative to present treatments for patients with heart failure and systolic dysfunction. An insightful review describes several new and appealing inotropic agents;[3] the mechanism of cardiac myosin activation, which directly affects the cross-bridge cycle and does not involve adrenergic pathways or affect myocyte intracellular calcium, is novel and intuitively attractive.

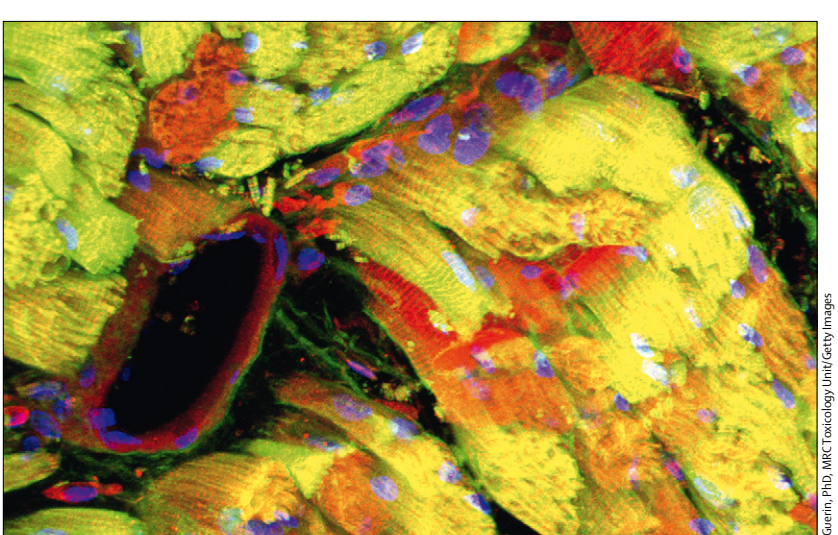
The two papers are complementary. The study by John Teerlink and colleagues[1] is the first-in-man assessment in healthy volunteers, and the subsequent study by John Cleland and colleagues[2] investigates the agent in patients with heart failure. Both reports focus on tolerability and provide dose-ranging information based on robust pharmacokinetic and pharmacodynamic data collection.

Conventional inotropic agents increase the rate at which ventricles develop pressure (dP/dt) but do not prolong the duration of systole. Treatment has not been shown to improve survival in chronic heart failure.[4] Myosin activation involves binding of a small molecule to the myosin catalytic domain to increase the transition rate of myosin into the strongly actin-bound force-generating state and permit more cross-bridges to form during systole.[5] An increase in the number of attachments of myosin heads to actin increases systolic ejection time and stroke volume, thereby increasing the extent of myocardial contraction without increasing the rate of contraction or myocardial oxygen consumption.[6] This increase in contraction should result in an energy efficient inotropic effect and improvement in heart failure symptoms. The mechanism makes sense and Teerlink and colleagues[1] use the captivating metaphor "more hands pulling on the rope".

A dose-ranging study of omecamtiv mecarbil in 34 healthy volunteers is reported by Teerlink and colleagues.[1] The primary efficacy measure was systolic ejection time, a sensitive and reliable measure of dose-related drug effect.[7] This effect is measured by echocardiogram and doppler imaging as the duration of the time-velocity integral signal sampled in the left ventricular outflow tract. The results show a convincing dose-related and plasma concentration-related prolongation of systolic ejection time, an increase in stroke volume and ejection fraction, and improved atrial contractile function.

Omecamtiv mecarbil was found to have a half-life of about 19 h; a steady-state concentration was not achieved during the 6 h infusion. As the authors concede, the goal of determining the maximum tolerated dose for future studies was only partly achieved. The agent was well tolerated across the doses assessed, but with a signal suggesting possible ischaemia at high-dose infusion due to excessive prolongation of systolic ejection time.

In the second study, Cleland and colleagues[2] report on the use of the cardiac myosin activator in a population of patients with mild heart failure. This investigation was a multicentre, double-blind, placebo-controlled, crossover, dose escalation study with 151 infusions of active drug or placebo in 45 patients, in five cohorts enrolled sequentially. Although apparently complex, the trial had two objectives. First, to assess safety and tolerability in patients with symptomatic heart failure and systolic dysfunction; and second, to assess dose effect on systolic ejection time, prolongation of which is believed to be the unique pharmacodynamic signature of myosin activation. Plasma concentrations of omecamtiv mecarbil were sampled frequently and



Confocal light micrograph of heart muscle

CJ Guerin, PhD, MRC Toxicology Unit/Getty Images

related to the safety and tolerability and pharmacodynamic profiles.

After identification of the target plasma concentration resulting in well-tolerated prolongation of systolic ejection time, and in view of the drug's moderate volume of distribution and long half-life, the investigators used an initial higher loading dose followed by a lower maintenance dose. The adverse-effect profile with regard to ischaemic episodes, presumably related to excessive prolongation of systolic ejection time, was closely related to high serum concentrations in both healthy volunteers and patients.

The results show an impressive correlation between plasma concentration and systolic ejection time. As postulated, this dose-related prolongation of ventricular systole resulted in significantly increased stroke volume and cardiac output, reductions in both systolic and diastolic ventricular volumes, and a more modest increase in the duration of atrial systole. Tolerability is reported in detail in both papers. Adverse effects suggestive of ischaemia happened only at the highest doses. Future efficacy studies should further explore the optimum loading dose and strength and duration of infusion.

In view of the mechanism by which omecamtiv mecarbil acts, some important theoretical caveats arise. With no change in heart rate, increased systolic ejection time must occur at the expense of diastole. Although patients with heart failure frequently have shortened systolic ejection time, some important events such as ventricular filling and coronary perfusion occur in diastole. Indeed, in most patients with heart failure, ischaemia is the cause.[8] Improvements in systolic emptying should not compromise diastolic function or coronary flow. In Cleland and colleagues' study,[2] heart rate actually decreased, which serves to attenuate the reduction in total diastolic time. The duration of atrial contraction also increased, suggesting an improvement in atrial myocardial function. The data presented in these two papers support further investigation of omecamtiv mecarbil's potential therapeutic role in appropriate patients. However, very few new agents have survived the most rigorous test, the randomised clinical trial assessing clinical outcomes.[9]

The need for parenteral therapy with omecamtiv mecarbil would define and limit the target population. Cleland and colleagues[2] discuss possible future development of an oral preparation. The authors also mention a new trial of parenteral therapy in patients with acute heart failure (NCT01300013). However, clinical research has not resulted in favourable outcomes for drugs assessed in patients hospitalised for acute decompensation.[10,11]

Acute heart failure often has multifaceted causes, and many patients have haemodynamic instability and acute coronary syndromes needing intervention; the patient's status is a moving target. Drug kinetics can be affected, and concurrent intravenous and oral polypharmacy is unavoidable. Potent parenteral diuretics, vasodilators, inotropes, and devices that result in effective short-term management of patients with acute heart failure are available.[12] Cardiac myosin activation should first be assessed in the large population with chronic systolic dysfunction, signs of heart failure, and New York Heart Association functional class III and IV symptoms. Subsequently, the potential role in patients managed in critical care, especially after cardiovascular surgery, should be explored.

So, in view of the attractive mechanistic theory, omecamtiv mecarbil's safety and tolerability profile, and these encouraging results, what would Einstein have suggested? Probably a controlled, randomised clinical trial assessing the effect on clinical outcomes. Let's find out how this theory performs in practice.

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I have served as an investigator in several clinical trials sponsored by Amgen and will be an investigator in a planned phase 2b trial involving omecamtiv mecarbil (NCT01300013).

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