

Familial dilated cardiomyopathy: from clinical presentation to molecular genetics

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Eur Heart J. 2000;21:1825-1832

This Clinical Perspective article outlines the clinical decisions and potential problems in diagnosis facing clinicians when a patient presents with a possible family history of dilated cardiomyopathy. Although diagnosis of dilated cardiomyopathy by clinical examination, electrocardiography, echocardiography, and angiography is relatively straightforward, family pedigree, noninvasive screening of informed consenting relatives, and possibly genetic analysis of affected subjects is required to accurately diagnose familial dilated cardiomyopathy. The article describes basic Mendelian and matrilinear law-driven methods for characterizing the disease by tracing the familial pedigree to understand the pattern of inheritance: for example, when a father, son, and daughter are all affected, an autosomal dominant disorder would be suspected, and X-linked, or recessive disease could be excluded. Similar familial formulae can be applied to diagnose autosomal dominant, recessive, and X-linked recessive disease. However, this is only the first step in a genetic approach to the disease. The diagnosis of familial cardiomyopathy is only the start of a detailed, and sometimes frustrating, investigative pathway. The etiopathogenic background of the disorder can be further dissected by examining a number of pertinent clinical signs.

In this article, Arbustini et al describe eight different phenotypes, detailing the clinical scenarios and outlining the steps necessary for their effective clinical and pathological identification. In their explanation of the diagnoses, the authors outline possible pitfalls in the methodology and the numerous problems associated with precise sampling when dealing with inheritable disorders of this type. This article further suggests an important link between the physician, the clinical staff, the pathology laboratory, and the research groups specializing in these disorders, since much of the diagnosis involves complex molecular investigation and can involve family members in order to precisely pinpoint the origins of the disease.

At present, though, it is recommended that information on patients should not rely on molecular genetics, but rather

on established clinical examination, assessment of the familial condition of the disease, identification of preclinical signs and asymptomatic patients, prevention of ventricular arrhythmias, and counseling.

Despite the fact that the knowledge on the molecular genetics of this disease is growing, the number of diagnoses that can be provided to patients is still limited to a few cardiomyopathies and rare general myopathies with heart involvement. The literature, currently, only contains a few articles about this subject and it is clear that major multi-center research projects are required if cardiologists are to plan properly for the prevention and eventual cure of familial dilated cardiomyopathy.

The authors of this article conclude by suggesting that a major scientific society, such as the European Society of Cardiology, should promote research in this field and provide the information needed to plan for useful preventive care strategies for dilated cardiomyopathy.

2000

After 15 years as world chess champion,
Gary Kasparov is beaten by his
25-year-old protégé, Vladimir Kramnik;
thousands march in Berlin in memory
of the 1938 anti-Jewish pogrom that presaged
the Holocaust; and an alcoholic brew mixed
with methanol to make it stronger kills
126 Kenyans and leaves a further 500
requiring hospital treatment



Randomized trial of an education and support intervention to prevent readmission of patients with heart failure

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J Am Coll Cardiol. 2002;39:83-89

One of the less frequently addressed issues in the management of heart failure is the high readmission rate to hospital after an initial inpatient episode. The authors quote a rate of readmission of up to 44% within 6 months of discharge. Among the causes of this high rate are poor compliance with medication and delays in seeking preventative care. This paper describes an intervention that teaches patients to understand their illness better and respond appropriately if deteriorating, with the aim of reducing the frequency of readmissions.

Consecutive admissions to the study hospital were screened for the presence of heart failure according to clinical or radiological parameters. Eighty-eight patients were enrolled into the study, and randomized to the study group or to the control group of usual medical care. Five educational domains were addressed, patient knowledge of the illness, the relationship between medications and illness, the relationship between health behavior and illness, knowledge of the early features of decompensation, and practicalities of obtaining necessary assistance. There were two phases of the intervention. In the first, an interview was conducted by an experienced cardiac nurse shortly after hospital discharge to identify the level of the patients' understanding of the above issues, thus providing a framework for future education. The second phase involved phone calls, initially weekly, but of reducing frequency, down to monthly, during which the nurse could reinforce education in the areas previously described. This contact was maintained over 12 months. In neither stage was an attempt made to perform extra clinical assessments, although, if appropriate, patients were advised to see their physician.

In comparing the study and control groups, the readmission rates were 56.8% and 81.8%, respectively (relative risk 0.69, $P=0.01$), and there was a similar reduction in the rate of multiple readmissions. A nonsignificant reduction in the death rate was observed in the treatment group. The Kaplan-Meier curves representing time to all-cause admission or death diverge early on, and the median times to such an event were 193 days in the treatment group and

126 days in the control cohort (relative risk 0.56, $P=0.03$). An estimate of the potential economic impact of this intervention was made, and although this intervention involves extra costs, these were heavily outweighed by the reduction in readmissions, with mean savings of nearly \$7000 per patient.

The key difference between this intervention and other previously described related strategies in the treatment of heart failure is that previous such studies have involved a more intensive provision of medical supervision. It appears that patient education and empowerment produce levels of benefit that approach those of more reactive programs of physician- or nurse-led therapeutic adjustment.

This study leaves some questions open. It is not clear how long the support needs to continue, nor whether there is an ongoing benefit to patients beyond 1 year. However, it is clear that there are very significant gains in terms of patient morbidity/mortality and cost savings, which are the result of a straightforward education program. As such, it seems reasonable to conclude that such initiatives could and should be introduced more widely, and form part of the standard management of patients hospitalized with heart failure.

2002

Horror writer Stephen King announces
he will retire when his contract expires after
the publication of five more books;
Argentina appoints its fifth President in two weeks;
and US reporter Pearl disappears while
investigating alleged shoe bomber Richard Reid's
ties to Moslem fundamentalists in Pakistan

Long-term trends in the incidence of and survival with heart failure

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N Engl J Med. 2002;347:1397-1402

Over recent decades, there have been significant advances in the treatment of hypertension, historically the leading cause of heart failure. In addition, the treatment of heart failure itself has witnessed major advances, with numerous randomized trials indicating the medications that reduce mortality. However, there has been a lack of clear evidence that these benefits have been translated into improvements in outcomes in the “real world.” In this paper, temporal trends among the Framingham study population are examined with regard to incidence of and survival with heart failure. This allows a longitudinal examination of these parameters over a 50-year period, with the inherent advantage that, in the Framingham study, a uniform set of diagnostic criteria and assessment has been utilized throughout.

The study began in 1948 with the enrollment of all members of the Framingham population aged 28 to 62 years. This cohort has been evaluated at 2-yearly intervals, and, in 1971, the descendants and their spouses were also enrolled, with reviews taking place slightly less frequently. The age-adjusted incidence of heart failure was higher at all times in males than females. In the former, the initial incidence was 627 per 100 000 person-years, compared with 420/100 000. The authors found little change in the incidence of heart failure in men over the last 50 years, while it has dropped by about one third in women. After controlling for various other risk factors, the risk of death has fallen by approximately one third over the same period in both sexes, with an overall trend of reduction in risk of death of 12% per decade (*P* for trend, 0.01 in men and 0.02 in women). Nevertheless, this leaves heart failure as a significant public health problem, and it remains a disease with a high mortality. The median 5-year survival rate in men in the 1990s was under 4 years, and in women it was 6 years, an improvement over the 2 and 4 years, respectively, seen in the 1950s.

In addressing the disparity between the sexes, the authors suggest that the falling incidence among women may relate to hypertension as a more frequent etiological factor in

women, with ischemic heart disease more common among men. There has been success in targeting and treating hypertension, but improvements in the treatment of myocardial infarction may have increased the number of survivors without affecting the numbers surviving with impaired left ventricular function. This, the authors suggest, is because there are now more survivors with residual damage, who are thus at risk of heart failure.

Three recent hospital-based studies of the mortality after hospitalization with heart failure have shown more substantial reductions in mortality than in this series. The authors highlight that in this study hospitalization was not a criterion for enrollment. They also suggest that hospital-based studies are open to a number of biases. Improved technology may result in lead-time bias, by allowing diagnosis at a less severe stage. The nature of diagnosis-based reimbursements to hospitals may influence the nature and number of diagnoses made.

There were some limitations to this study, including the predominance of whites among the subjects, meaning that one may not necessarily extrapolate these results to other racial groups. Patients in the Framingham Heart Study may have had better medical access than other patients, leading to better outcomes. Despite these concerns, one may conclude that the incidence of heart failure among women has decreased and that improved survival has occurred in both sexes over the last 50 years.

2002

A study on animal intelligence reveals that Californian sea lions may have the best memory of all nonhuman creatures; the Pope canonizes Opus Dei founder Josemaria Escrivá de Balaguer; and a masked gunman in Queens, New York, shoots run-DMC D. J. Jason Mizell aka Jam Master Jay



Differential gene expression and genomic patient stratification following left ventricular assist device support

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J Am Coll Cardiol. 2003;41:1096-1106

Donor organs required for heart transplantation are in limited supply and for many patients the wait for transplant surgery proves too long, with fatal deterioration before organ availability. A treatment to help maintain an adequate circulation is the use of a left ventricular assist device (LVAD). LVADs have previously been shown to reduce mortality and are thought to lead to reverse remodeling of myocardial structure and function.

This article seeks to determine whether mechanically unloading the failing human heart with an LVAD results in significant change in left ventricular gene expression using gene microarray technology. Previous reports have looked at the expression of particular genes in response to this treatment and have led to the understanding that this useful therapy can lead to significant changes in gene and protein expression. However, using oligonucleotide microarray technology, which can detect approximately 6800 genes or novel clones with homology to known genes, the authors were able to examine many more genetic pathways, thus gaining a greater insight into some of the molecular mechanisms that may be involved in LVAD-mediated myocardial recovery.

Statistical analysis of gene arrays from 6 male patients at the time of LVAD placement and at myocardial explantation revealed a large number of genes that were upregulated or downregulated in response to treatment. Interestingly, further statistical analysis revealed a clear demarcation between gene expression profiles pre-LVAD and post-LVAD, and also identified two distinct groups among the pre-LVAD failing hearts depending on their etiology, determined both clinically and pathologically after explantation. In particular, the pre-LVAD patients with nonischemic, idiopathic dilated cardiomyopathy had distinctly different myocardial gene expression post-LVAD, whereas those patients exhibiting ischemic cardiomyopathy had similar gene profiles both pre-LVAD and post-LVAD. Examination of this phenomenon revealed that out of the 900 or so genes whose expression was modified during the treatment, only 16 were shared between these two groups. This underscores the divergent

baseline phenotypes and responses to LVAD-mediated reverse remodeling that occur in ischemic and nonischemic cardiomyopathies.

In addition, genes determined to have been significantly regulated were sorted according to their biological function. Although the data obtained were not shown to be statistically different, it is of interest that there was an enhancement in the percentage of metabolic genes changed significantly following LVAD support, thus supporting the authors' hypothesis that LVAD enhances reverse myocardial remodeling.

This study demonstrates the ability to distinguish patients' LVAD status and heart failure etiology using oligonucleotide microarrays. The differential gene expression identified in the study further demonstrates that phenotypic changes that occur following LVAD support are associated with genotypic changes in the form of significantly altered myocardial gene expression profiles. Importantly, in their closing remarks, the authors suggest that microarray technology might be used to facilitate the prediction of an individual patient's response to LVAD therapy.

2003

Islamic cleric sheik Abdel Majid al-Khoei, a prominent Shiite, is murdered at the Najaf mosque a week after returning to Iraq from exile; scientists at the British Columbia Cancer Agency decipher the SARS genome, demonstrating it to be a completely new coronavirus; and the Rijksmuseum in Amsterdam is closed for an indefinite period after asbestos is found in the building during a routine inspection

Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure

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J Am Coll Cardiol. 2003;41:1797-1804

Despite the introduction of many new therapies for the treatment of chronic heart failure, morbidity and mortality remain high. It is clear, however, that patients with this condition form a heterogeneous group and various strategies have been employed to distinguish between those at different levels of risk. Many of these strategies use measures that have inherent limitations. Peak oxygen consumption is demanding to record, and most suited to use in the assessment of the stable, moderately effected patient. The New York Heart Association (NYHA) classification, based on symptoms, is intrinsically subjective. Laboratory markers such as neurohormonal peptides have been demonstrated to be of predictive value at a population level, but their role in guiding individual management is less clear.

In 1976, Forrester et al described 4 hemodynamic profiles based on pulmonary artery (PA) catheterization parameters. These profiles segregated patients according to the presence or absence of congestion (pulmonary capillary wedge pressure threshold of 18 mm Hg), and adequacy of perfusion (cardiac index threshold 2.2 L/min/m²). Forrester's original paper demonstrated that the prognosis of patients post-acute myocardial infarction correlated with their subgroup. The hypothesis examined in Nohria's paper is that a similar classification based on clinical examination might be useful in guiding management.

Of the 452 patients enrolled into the study, the majority were admitted with decompensation of heart failure (49%), but there were significant numbers admitted with arrhythmias, angina, and for heart transplantation evaluation. Patients were categorized according to the presence of congestion and adequacy of perfusion. Congestion (wet) was defined by the presence of recent history of orthopnea, elevation of the jugular venous pressure, hepatojugular reflux, peripheral edema, leftward radiation of the pulmonary heart sounds, or a square-wave blood pressure response to a Valsalva maneuver. Impaired perfusion (cold) was defined by the presence of a narrow proportional pulse pressure (pulse pressure/SBP <25%), pulsus alternans, symptomatic hypotension, cool extremities, or impaired cognitive

function. This defined 4 groups: dry-warm (A), wet-warm (B), wet-cold (C), and dry-cold (L). Follow-up was for at least 12 months, with end points of time to death and the combined end point of time to death or heart transplantation.

There were clear and significant differences between the different groups, (although group L was too small to allow statistical analysis). Compared with group A, the hazard ratios were 3.66 for group C ($P < 0.001$) and 2.10 for group B ($P < 0.003$). Further stratification of these groups using the NYHA classification showed that groups B and C tended to co-segregate with classes III and IV. However, these clinical profiles were independent predictors of mortality. In a subset of patients investigated using the PA catheter, there was good correlation with the clinical groups.

The authors propose that these profiles may aid in the selection of appropriate therapy, in the same way that the PA catheter does, although accepting that there are no data to support this strategy. For example, profile A (dry-warm) may be likely to tolerate the introduction and uptitration of β -blockers, whereas, in group B, one would not do this until the patient had stabilized and returned to group A, and in Group C, one might consider reduction or cessation of such drugs. In addition, it is proposed that since these profiles are independent predictors of outcome, they may prove useful tools in the selection of patients for clinical trials.

2003

Scientists create a mule, named Idaho Gem, from a cell from a mule fetus and a horse egg; the Old Man of the Mountain, a 700-ton granite formation, falls from its perch at New Hampshire's Franconia Notch; and the military regime in Burma announces that Aung San Suu Kyi and other members of Burma's National League for Democracy are in protective custody



Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study

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Lancet. 2003;361:1843-1848

This paper describes the long-term outcomes of patients recruited into the Studies Of Left Ventricular Dysfunction (SOLVD). The original study recruited patients with left ventricular (LV) dysfunction (ejection fraction $\leq 35\%$) and compared outcomes on enalapril vs placebo in patients with and without overt heart failure. Although short-term benefits of angiotensin-converting enzyme (ACE) inhibitors in the treatment of LV dysfunction had been observed, the longer-term effects were unknown. Furthermore, it was unclear whether such a benefit could be enhanced by initiating treatment prior to the development of symptoms.

A total of roughly 7000 patients were entered into the treatment or prevention arm based on whether or not they were already receiving heart failure therapy or had symptoms of heart failure. All were randomized to enalapril or placebo, and followed for a mean duration of 3.2 years.

The prevention trial showed a relative risk reduction in the combined end point of death or development of heart failure of 29%, ($P < 0.001$). There was no significant reduction in mortality alone in this asymptomatic group, whereas in the treatment group, the death rate was reduced by 16% ($P = 0.0036$). It was suggested that those treated with enalapril for heart failure gained 0.4 years of life expectancy.

The current manuscript reviews the outcomes after 12 years of follow-up. Despite this long follow-up period, outcomes were known in 99.8% of the original participants. In the prevention study, death occurred in 56.4% in the placebo group, compared with 50.9% in the enalapril group ($P = 0.001$), with an increase in median survival from 10.3 to 11.1 years ($P = 0.05$). Furthermore, the survival curves continued to diverge for the whole period even though patients were not necessarily on their assigned study medication after the end of the trial. In the treatment study, the death rate was slightly lower in the enalapril group than the placebo, but most patients were dead (79.8% and 80.8%, respectively). The survival curves, though initially inevitably diverging, converged toward the end of follow-up, as shown by the median survival (5.5 and 4.8 years, respectively). There were

no differences in survival among the prespecified subgroups according to age, gender, ethnicity, cause of LV dysfunction, hypertension, diabetes mellitus, and New York Heart Association class at baseline. The benefit was seen to be greater in those with lower ejection fractions.

This extension of the original study has shown a benefit in the prevention arm, and suggests that 56 deaths could be prevented by the treatment of 1000 patients for 3 years. It is noted that after the first phase of the trial, patients were in many cases started on ACE inhibitors, as recommended by the trial committee, with a probable reduction in the difference observed between treated and placebo groups. The reduction in mortality with enalapril is felt to be possibly due to a reduction in the rate of nonfatal myocardial infarction during the initial study, with subsequently reduced risk of progression to heart failure. The authors discuss the convergence of the survival curves in the treatment group and offer a number of suggestions. There was a significant reduction in the number of cardiac deaths and a similar excess of noncardiac deaths, so they postulate that when cardiac death is prevented, there may be exposure to alternative competing causes of death.

The authors conclude that treatment for 4 years with enalapril in all patients with LV dysfunction reduces the risk of death over the long term

2003

Indian Prime Minister Atal Bihari Vajpayee restores civilian air travel between his country and Pakistan in an effort to ease tensions;
more than 800 000 French public workers stage a 1-day strike to protest pension reforms;
and Nepal confers honorary citizenship on Sir Edmund Hillary to mark the golden jubilee of the first ascent of Mount Everest

Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL)

D. L. Mann, J. J. McMurray, M. Packer, K. Swedberg, J. S. Borer, W. S. Colucci, J. Dijan, H. Drexler, A. Feldman, L. Kober, et al

Circulation. 2004;109:1594-1602

Observation of elevated levels of tumor necrosis factor (TNF) in heart failure led to investigations into its possible role in the pathophysiology of the condition. A heart failure phenotype is seen when TNF is administered to experimental animals and in transgenic animals that overexpress TNF. High levels of TNF have been observed in a number of disparate conditions, including ankylosing spondylitis, rheumatoid arthritis, and psoriasis. Etanercept is a recombinant human TNF receptor that binds to soluble (circulating) TNF, causing functional inactivation by preventing the binding of TNF to cell surface receptors. Trials of it in the inflammatory conditions mentioned above resulted in clinical improvements, leading to trials in heart failure. Small studies suggested that there was a benefit in terms of left ventricular function, and thus larger clinical trials were designed.

This paper reports on the combined results of two studies designed to determine the effects on patients' functional capacity and morbidity/mortality. The studies had similar designs, differing mainly by geographical locality: RECOVER took place in Europe, Australasia, and Israel, while RENAISSANCE was undertaken in North America. Patients with ischemic or nonischemic heart failure graded between New York Heart Association class II and IV, with ejection fraction $\leq 30\%$, were assigned to receive placebo or etanercept 25 mg SC once, twice, or three times a week. Both studies were terminated early (RECOVER after 6 months; RENAISSANCE after 12 months), due to failure to demonstrate benefit. There was no evidence of an excess mortality in the etanercept groups, but there was certainly no benefit. Among prespecified subgroups, no differences were observed in the effects of etanercept.

To offer some possible explanation for this apparent lack of benefit, the authors briefly discussed the possibility that TNF is not important in the pathogenesis of heart failure, and the elevated levels are a consequence of heart failure, or of chance. Second, although the conditions described above have been seen to improve with anti-TNF therapy, others associated with elevated levels, including Crohn's

disease and systemic sepsis, do not respond. This implies that there may be a more complicated network of cytokines, and the removal of a single component may be insufficient to result in benefit. This could be assessed by the measurement of TNF bioactivity, as well as the levels of other circulating cytokines. This would also be useful in investigating whether the dose of antagonist was sufficient to neutralize the effects of TNF. The authors observed that among those patients who worsened, disproportionately represented were the patients who had been exposed to etanercept for the longest duration. They wondered whether there is an early period of benefit, as seen in the pilot studies, followed by a period where continuation of etanercept is detrimental. This might be caused by a phenomenon whereby etanercept stabilizes a biologically active (trimeric) form of TNF and thus paradoxically acts as a TNF potentiator. The final possibility is that TNF might play a useful role in maintaining cardiovascular stability, and prolonged blockade might therefore be deleterious.

Infliximab is a monoclonal antibody to TNF, recently employed in the Anti-TNF- α in Congestive Heart Failure (ATTACH) study. Circulating TNF was neutralized, and cell-bound TNF resulted in cell lysis. This study reported an increase in death and heart failure hospitalization. Although infliximab and etanercept act in different ways, there must now be concern over the targeting of TNF in this way. Future therapies are likely to be directed at other components of the inflammatory cascade, or at multiple components.

2004

The discovery of a cat buried with its owner in a Neolithic grave on Cyprus suggests domestication of cats began at least 9500 years ago; the popular search engine "Google" announces it will offer shares to the public in late 2004; and the African National Congress wins South Africa's general election claiming about 70% of the vote



Regenerative capacity of the myocardium: implications for treatment of heart failure

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Lancet. 2004;363:1306-1313

This review article describes in some depth novel approaches to the management of heart failure and discusses the rationale for, as well as the limitations of, each treatment. Von Harsdorf et al introduce a fictitious, but clinically typical, patient: a 46-year-old man with a recent diagnosis of acute myocardial infarction (MI). Having survived the acute period of MI the patient has substantial irreversible myocardial damage and exhibits symptoms of heart failure due to the remodeling process. This is characterized by structural changes within the healthy area of the heart both adjacent to, and remote from, the damaged area. The authors go on to describe possible options for the patient's treatment and outline four possible alternatives: conventional drug therapy; cardiomyocyte replication therapy; cloning of artificial organs, and organ regeneration via stem cells.

Drug therapy, referred to as the "dinosaur approach," involves the use of pharmacological blockade of the compensatory systems increasing myocardial workload. Such approaches are known to prolong life in patients with heart failure. However, such therapy is limited since it will not cure the patient, the myocardium will remain damaged, since mammalian hearts are not able to significantly regenerate lost tissue. Therefore, conventional therapy may only serve to prolong the inevitable progress of heart failure. Leading on from this approach, the authors describe a novel therapy by which the patient's myocardial cells are encouraged regenerate and replace, or prevent the generation of, scar tissue, thus avoiding long-term drug therapy. Although not currently available, the rationale behind this concept is well defined in the article. Modification of the adult myocyte cell cycle is possible *in vitro*; however, we do not fully understand how an adult heart will cope with reintroduction of proliferative capacity. Moreover, control of cardiomyocyte replication will present a bigger challenge to modern biotechnology.

Although cloning of human tissue is not yet possible for ethical reasons, the concept of regenerating an immunologically compatible organ from nuclei taken from a skin biop-

sy is also discussed. The "Dolly approach," as it is termed, describes the concept of manufacturing a copy of the patient's heart around a biodegradable scaffold. Although there is no evidence to support this process it is, at least theoretically, possible, but would require an intimate knowledge of cardiomyocyte differentiation, which is currently absent. Akin to organ cloning, there is much controversy surrounding stem cell therapy. Stem cells have the innate ability to transform into any cell type given the right environmental factors. The authors are cautious to expand on the efficacy of this approach, as there have not been any large controlled studies using stem cells.

The authors suggest the use of cautious optimism when it comes to the development of these new therapies: so much more needs to be known before carefully controlled clinical trials of any of these new therapies can be undertaken.

2004

At least 10 bombs explode on four commuter trains in Madrid during the rush hour, killing 191 people and wounding more than a thousand; in the biggest expansion in its 55-year history, NATO formally admits seven new countries, from the former Iron Curtain zone; and NASA announces that its robot explorer Opportunity has detected signs that water once covered rocks in a small crater on Mars

Do we understand who benefits from resynchronisation therapy?

O. A. Breithardt, P. Claus, G. R. Sutherland

Eur Heart J. 2004;25:535-536

Cardiac resynchronization therapy (CRT) is now an accepted tool in the treatment of severe left ventricular dysfunction. In this editorial, Breithardt et al explain that despite growing use of this technique, there is evidence that up to 30% of those treated fail to respond. The underlying strategy centers on reducing the contraction delay between each ventricle and/or between regions of the left ventricle. There is evidence that both these forms of delay may be important. Improved synchrony is achieved by preexcitation of the late-activated regions through the implantation of left ventricular or biventricular pacing electrodes.

The authors explain that the tools used to select the patients may be insufficiently precise to predict who will respond. In particular, it is those cardiac segments with the most delayed onset of contraction that need to be identified. The ideal tool to achieve such identification remains an area of controversy. Similarly, there is a lack of consensus as to whether intraventricular or interventricular dyssynchrony is more responsive to CRT.

The authors outline the criteria for selecting an ideal imaging technique that will determine clinically important abnormalities in the timing of onset of regional ventricular active force development. Such a technique also would need to be easy to interpret, reproducible, and cost-effective. A high sampling rate is also critical, since the intervals responsible for delay are extremely short. Currently, the technique that best fulfills these criteria is echocardiography. A fundamental question is what degree of delay is sufficient to be labelled abnormal and likely to benefit from correction. In addition, there are a number of methods for measuring this delay. Regional longitudinal systolic velocity profiles may be obtained from all ventricular segments, but do not indicate the regional contractility. The more novel techniques of strain rate and strain estimation imaging reflect contractility better, although technology does not allow their application in thin walled segments.

The cardiac event to be used as the marker to determine delay is clearly very significant. Some researchers advocate

the time-to-onset of regional systolic motion, whereas others propose the time-to-peak systolic motion, or measure time to postsystolic events. The authors conclude that the first of these options is preferable, since the presence of a plateau in the velocity profile will create possible errors in determining the exact time of peak systolic motion, and the earlier a parameter is measured within the cardiac cycle, the less prone it is to distortion introduced by alterations in loading conditions or segmental interactions.

Once having determined the presence of dyssynchrony by selecting a reliable technique and an appropriate parameter to measure, the authors highlight further important potential pitfalls relating to the underlying pathophysiology. For example, resynchronization therapy may reduce postsystolic shortening (PSS). PSS occurs in left bundle branch block due to delayed segment activation, an appropriate target for resynchronization. However, it may similarly occur in the presence of ischemia, when it is a passive phenomenon, and there will be no response to CRT.

The authors conclude that echocardiography is fundamental in the selection of patients suitable for this therapy. The first line of selection requires an abnormal QRS duration, with echocardiographic confirmation of dyssynchrony. The more precise evaluation requires the use of the modalities discussed above, but large controlled trials are required to determine which is the optimal technique.

2004

Pakistani scientist Abdul Qadeer Khan admits passing on nuclear weapon technology to other countries; new Spanish Prime Minister José Luis Rodríguez Zapatero orders the recall of all Spanish soldiers from Iraq; and North Korea's reclusive leader, Kim Jong-Il, arrives in Beijing for talks on his country's future



Hypertrophic cardiomyopathy

P. Elliott, W. J. McKenna

Lancet. 2004;363:1881-1891

Hypertrophic cardiomyopathy (HCM) was first described in 1869. Although initial research focused on the morphology of the disorder, as evidence for an inherited pattern emerged, the focus turned to genetic studies, culminating in the first culprit gene mutation in the β -myosin heavy chain coding sequence.

Many further mutations in genes encoding this and other components of the contractile apparatus have since been discovered, suggesting that this is the unifying factor in the disparate group of phenotypes that constitute HCM. Detailed research into genotype-phenotype correlations has failed to demonstrate consistent associations.

HCM is uncommon in children, and although a number of conditions cause a similar pattern of disease in adults, attempts to distinguish the two should be made. The characteristic hypertrophy of the septum may also extend to other parts of the left ventricular wall, and rarely the right ventricle, but not the right ventricle alone. The histological hallmark is myocyte disarray.

One of the difficulties with the management of this condition is that there may be few symptoms, and these may be nonspecific. Similarly, the examination may be unrevealing. A bisferious pulse indicates dynamic outflow obstruction, which will be associated with a systolic flow murmur. Mitral regurgitation may also be evident, relating to the anterior movement of the mitral valve during systole.

The echocardiogram is the major diagnostic tool, and any wall segment with a thickness of more than 15 mm without an alternative explanation is diagnostic. In the nonblack patient, it is unusual for such hypertrophy to occur due to hypertension unless this is severe. Another major diagnostic conundrum is the athlete with hypertrophy, in whom it may be difficult to make a certain diagnosis, though in this group, both ventricles are usually enlarged. Dynamic obstruction may also be revealed using echocardiography. Further echocardiographic parameters are discussed, including diastolic assessment and tissue Doppler imaging.

The role of cardiac magnetic resonance imaging in clinical practice is generally similar to that of echocardiography.

Metabolic exercise testing usually reveals reduced peak oxygen consumption, while a premature lactic acidosis may be indicative of mitochondrial myopathy. Symptoms relating to outflow tract obstruction may be treated with β -blockers, or occasionally disopyramide or verapamil. If drug therapy is unsuccessful, septal myectomy or septal alcohol ablation may be performed. The treatment of heart failure in HCM mirrors that due to other causes and, as atrial fibrillation may cause significant deterioration in HCM, restoration of sinus rhythm is important. There is a predisposition to sudden death in HCM, thought to be due to ventricular arrhythmia in most cases. Implantable cardioverter-defibrillators may help to prevent such deaths, and should be offered to those at high risk. A major challenge exists to detect these individuals in advance of a first event. The major risk predictors include a family history of sudden cardiac death, unexplained syncope, non-sustained ventricular tachycardia on Holter monitoring, severe hypertrophy (>30 mm), and a flat blood pressure response during upright exercise.

Finally, the article discusses the need for genetic counseling and suggests that an ECG and echocardiogram should be performed in first-degree relatives of affected individuals, and that echocardiography should be repeated every 5 years, because of the possibility of late-onset disease.

2004

The Cassini spacecraft inserts into orbit around Saturn and transmits detailed photographs of the planet's complex ring system; Mike Melvil pilots "SpaceShipOne" into space, becoming the first person to do so in a privately developed aircraft; and dozens of Colombian coca farmers are killed by Marxist rebels