Myo-pericardial Disease

BC-01

ELECTROCARDIOGRAPHY IN APICAL HYPERTROPHIC CARDIOMYOPATHY

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Apical hypertrophy is now categorized as apical hypertrophic cardiomyopathy (APH) in a group of hypertrophic cardiomyopathy (HCM). In these varieties, APH is the most frequent HCM in my country and has a distinct electrocardiographic feature, which includes giant negative T waves (GNT) in the left precordial leads (usually V4, occasionally V5) and left ventricular hypertrophy suggested by high voltage in these leads. The negativity of the T waves is said to be greater than -1.0mV (-10mm) according to several authors, but this arbitrary definition is reserved to be verified by the long-standing study. The purpose of the present report is to solve the mystery of the GNT in APH based on the follow-up study of 30 years in a large group of patients.

The mystery of the electrocardiogram in APH is multiple:

1. When does the abnormality start?
2. What is the first abnormality?
3. When does the typical pattern develop?
4. Is the start gradual or sudden?
5. Are there any diurnal changes in the T waves?
6. Does exercise induce the change of the T waves?
7. How deep is the maximal inversion of the T waves?
8. Does the depth of the T waves relate to the grade of hypertrophy?
9. What is the genesis of the occasionally observed short P-R interval ?
10. Does bundle branch block associate with GNT?
11. Are there the cases with APH without GNT?
12. Are there the cases with HCM with GNT?
13. Should the GNT of APH accompany with left ventricular high voltage?
14. How long the GNT persist? ie, when the decay of the typical ECG change start?
15. What is the sequelae of the thickened apical muscle and the fate of the ECG?
16. What is the most serious arrhythmia complicated?
17. Is the ECG helpful to predict the therapy and prognosis?

Summarizing the answers questioned based on the over 200 patients, in whom 132 patients were followed more than 1 year (1 to 31 years), APH was exclusively encountered in middle-aged men by incidental health check including ECG in nearly all cases. Retrospectively examined, development of the GNT from the normal ECG required several years, and once it was established, it did not change significantly, except for minor diurnal variation. Sudden appearance of GNT within a year or several months may be observed in exceptional cases. Following long period of time, disappearance of the GNT may occur slowly, though APH remained constant. Therefore, APH may exist without GNT and left ventricular hypertrophy pattern. During progress, incomplete and then complete right bundle branch block pattern occasionally appeared. Although the prognosis of APH is benign, electrocardiographic catastrophe represented by the pattern of myocardial infarction and ventricular aneurysm (2 cases) and atrial fibrillation (5 cases) disclosed by Holter monitoring suggested the poor prognosis and indicated the prompt and intensive therapy.

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BC-02

NONINVASIVE DIAGNOSIS IN PERICARDIAL DISEASE: MULTIPLE METHODOLOGIES

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Noninvasive diagnosis complements clinical and supplements invasive investigations, replacing some. The most important pericardiopathies include: acute pericarditis, effusion, tamponade, constriction, pericardial masses, and pseudoaneurysms. Diagnosis and pathophysiology can be determined noninvasively, including chest X-ray (CXR), electrocardiogram (ECG), mechanocardiography (MCG), systolic (STI) and diastolic (DTI) time intervals and radionuclide imaging (RNI); and: echocardiography (echo), Doppler flows, computed tomography (CT), and magnetic resonance imaging (MRI) (Table). ECG is useful in acute pericarditis and tamponade; MCG in acute pericarditis, tamponade and constriction; STI and DTI in effusion, tamponade and constriction; RNI in acute pericarditis and effusion. Echo and Doppler are ideal for effusion, tamponade, constriction, pericardial masses and pseudoaneurysm. CT and MRI demonstrate effusion, constriction, masses and pseudoaneurysms. Lateral CXRs may show fat lines in effusions. Phonocardiography documents rubs and heart sounds. ECG in acute pericarditis is virtually diagnostic in over 50%. RNI is limited, e.g. Gallium uptake in leukocytes. Sequelae of acute pericarditis include effusion with and without tamponade and effusive-constrictive pericarditis. ECGs in large effusions may show low voltage. RNI shows cardiac radioactivity surrounded by a "dead" (effusion) zone. Echo is optimal---inexpensive, readily available, dynamic. STI show excessive respiratory changes in tamponade and lax effusions. Clinical physiology of cardiac compression (tamponade and constriction) is elucidated noninvasively, especially by echo-Doppler. RNI and MCG demonstrate pulses (jugular; carotid), sounds; STI and DTI, CXR, CT and MRI are adjunctive. Recently investigated are echo B-mode, color-encoded tissue Doppler, intravenous contrast echo-Doppler, mitral annular velocity and ultrasonic tissue backscatter. Doppler shows comparable respiratory changes in tamponade and constriction. ECG in tamponade may show electric alternation, due to cardiac swinging. Pulsus paradoxus appears in invasive and noninvasive pulses. Echo with right sided chamber collapses suggests tamponade. (Combined right and left atrial collapse is virtually pathognomic.) Among pericardial masses, echo, MRI and CT shows fibrin, clots in and adhesions in fluid, which can constrict. CXR, CT and URI showing pericardial calcification suggest constriction pericarditis. Good jugular pulses show a large y descent simultaneous with the PCG's S3. MRI and 2-D echo show superior and inferior vena cava dilation with reproduced inspiratory narrowing. M-mode echo documents septal shifts, atrial and early diastolic septal notches and septal bounce of constriction and reversal of the hepatic vein Doppler A wave

Pericardial masses include congenital cysts, on CXR, confirmed by CT, MRI, or echo. Mesothelioma is well shown by MRI and CT, which identify most tumors. Pseudoaneursym is seen as a space usually adjacent to the left ventricle on echo; spectral and color Doppler document outward systolic and inward diastolic flow

Principal Pericardial Diseases: Noninvasive Diagnosis

	Acute Pericarditis	Effusion	Tamponade	Constriction	Masses	Pseudo-aneurysm
ECG	+		+			
MCG	+		+	+		
STI/DTI		+	+	+		
RNI	+	+				
Echo		+	+	+	+	+
Doppler		+	+			+
CT		+		+	+	+
MRI		+		+	+	+

BC-03

HEART RATE VARIABILITY. METHODS AND APPLICATIONS

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Introduction

Activity of the nerves of the autonomic nervous system (ANS) influence heart rate and blood pressure by means of two pathways: the sympathetic pathway and the vagal pathway. Simply put, the sympathetic drive causes a cardio-acceleration, vagal tone causes a deceleration in heart rate. Feedback is provided by the baroreflex mechanism, controlled by baroreceptors located in the most important arteries.
In some more detail: the ANS describes those nerves that are concerned predominantly with the regulation of bodily functions, including the cardiovascular system. The ANS can be divided in sympathetic and parasympathetic nerves. The parasympathetic supply to the heart runs in the vagal nerves. Both the sinoatrial and atrioventricular nodes are richly innervated by parasympathetic nerve fibers. Activity in these nerves (acetylcholine infusion) slows the heart rate down. Sympathetic innervation supplies all regions of the heart: pacemaker tissue, conduction tissue and both atrial and ventricular myocardium. Increased sympathetic activity (norepinephrine infusion) increases heart rate.

Heart rate variability in general

Autonomic cardiovascular control can easily be measured non-invasively by means of continuous electrocardiogram (ECG) (see figure 1; left: ECG; right: tachogram) and blood pressure recordings. The beat-to-beat variability of heart rate (HRV) and blood pressure (BPV) allows to measure both sympathetic and vagal influences on the heart. A combination of HRV and BPV provides an index of the baroreflex mechanisms.
Time domain analysis. The simplest way to describe heart rate variability, or cardiovascular variability in general, is by means of statistical measurements (mean, standard deviation, ...= time domain analysis).
Frequency domain analysis. Spectral analysis (figure 2) however shows clearly the distinction between sympathetic and vagal modulation. Different frequency bands correspond to modulation of the branches of the autonomic nervous system. Low frequency oscillations of heart rate (LF: 0.04-0.15 Hz) correspond predominantly to sympathetic modulation, but also vagal influences and the baroreflex influence this area, while high frequency fluctuations (HF: 0.16-0.4 Hz) are related to vagal or parasympathetic modulation of heart rate. Recently, non-linear analysis techniques have been used to describe the non-linear content of the variability signals.
Heart rate variability (HRV) is a non-invasive technique that provides an index of cardiac autonomic regulation through measurement of beat to beat variations of heart rate. Furthermore HRV has been shown to decrease with ageing. In a previous study we have demonstrated that the autonomic modulation decreases gradually up to the age of 45 years. After this age the autonomic modulation remains stable.
Decreased HRV is associated with an increased risk of cardiac events in clinically disease-free patients. Similarly, after myocardial infarction, low HRV is correlated with high mortality in patients.

***Figure 1:** Generation of the tachogram*

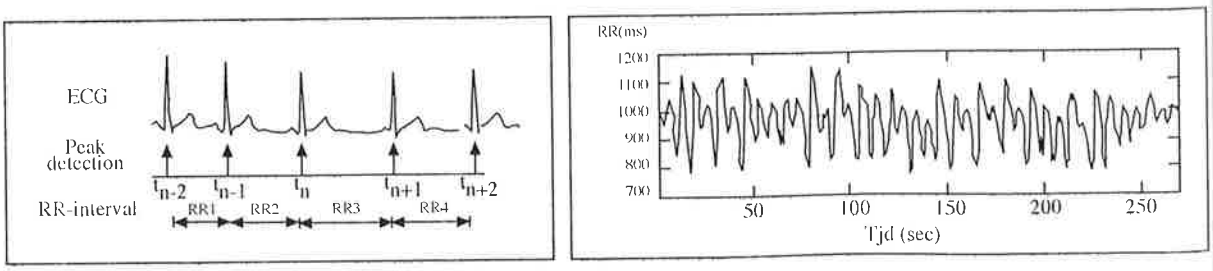
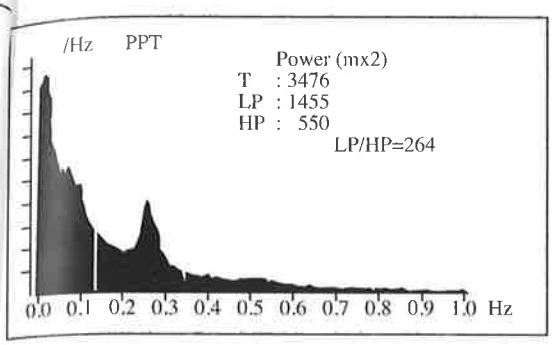


Figure 2: HRV power spectrum with LF and HF component



Applications of HRV

Digital signal analysis techniques and the software necessary for computing the HRV, BPV and baroreflex indices, indicating the amount of sympathetic and parasympathetic modulation, have been developed and perfected at the Laboratory of Experimental Cardiology over the past years. HRV methodology has been applied in clinical studies in which cardiac autonomic activity plays an important role.

Following topics have been studied and some results were already published or are in progress:

- evolution of HRV as a function of ageing in a healthy population (276 subjects between 18 and 71 years of age) and gender (135 women and 141 men)
- influence of behaviour on HRV: in 276 subjects, HRV parameters were compared with coping strategies
- influence of athletic training on HRV[2] between control subjects (N=10), aerobic trained (N=10), anaerobic trained (N=8) and rugby players (N=8)
- effect of long-term physical exercise on HRV parameters in an elderly population (55+) (N=15)
- tilt test for syncope patients and tilt test study of a normal population. In total 136 patients with multiple episodes of syncope were investigated with tilt test and HRV results compared to tilt test in 20 normal subjects,
- HRV in patients after heart transplantation (N=107)[3]
  Association between restoration of autonomic modulation in the native sinus node and haemodynamic improvement after cardiac transplantation. Transplantation 73: 1614-1620, 2002, evolution of the autonomic modulation in the first year after heart transplantation and 10-year follow-up of cardiac transplant patients (N=226)
- HRV studies in animals: a model for centrally or peripherally administered drugs in rats (N=73) using time and frequency domain methods (PhD thesis D. Ramaekers 1999) was developed. The results for the influence of autonomic blockade on non-linear indices of HRV and BPV in rats are currently submitted for publication in a peer-reviewed journal. Also a model for heart failure in sheep (N=12) was developed.
- Evolution of HRV during maturing of the autonomic nervous system in chicken embryos.
- Application of HRV for cardiovascular space physiology. HRV has been determined during simulation of weightlessness (with head-out-of-water immersion method, N=25), during weightlessness obtained during parabolic flight (N=12)[4] and during the Odissea Mission (Belgian Soyuz flight) in 3 cosmonauts.

Besides the classical analysis methods such as Fast Fourier Analysis, also parametric methods have been developed (autoregression), wavelet decomposition and joint time-frequency analysis, Wigner-Ville (SWVD) transform and instantaneous center frequency.

Non-linear analysis methods related to chaos theory (attractors, 1/f behaviour of the power spectrum, fractal- and correlation dimension, Poincaré- and higher order moment plots, approximate entropy, detrended fluctuation analysis, Lyapunov exponents) have been implemented (PhD thesis F Beckers 2002).

Conclusions

Measurement of HRV parameters provides a useful tool for the assessment of the status of the cardiac autonomic regulation. It can easily be performed from ECG and continuous blood pressure recordings and appropriate data analysis, in time domain, frequency domain or with non-linear methods. HRV can be used as well for clinical assessment as for basic research in the field of cardiovascular autonomic function.

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BC-04

T-WAVE ALTERNANS AND MORPHOLOGY

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Identification of patients at high risk of life-threatening ventricular tachyarrhythmias represents one of the most challenging issue in cardiology especially after myocardial infarction[1]. Programmed electrical stimulation has been used to assess vulnerability to life-threatening ventricular arrhythmias. However, this invasive technique has appeared to be of limited prognostic value in these patients[2]. Non-invasive methods to identify increased risk for ventricular arrhythmias include assessment of heart rate variability[3], baroreflex sensitivity testing[4], QT dispersion[5], and the signal-averaged ECG (SAECG)[6]. Poor sensitivity and low positive predictive value are common limitations of these noninvasive indexes, that is why new markers are necessary to identify patient who susceptible to major cardiac arrhythmias.

T-wave alternans as a new risk strafication marker

T-Wave alternans (TWA) can be defined as beat to beat changes in T-wave morphology that occur during regular rhythm[7]. The clinical observations and experiments on the animals show that TWA is usually associated with a risk of ventricular fibrillation[8-9]. Thus it may be used as a non-invasive marker of susceptibility to life-threatening ventricular arrhythmias[9-10].

The clinical observation of TWA, however, is not so easy, and so common, and in most cases, the alternans magnitude is in microvolt level, and visual detection becomes impossible[8].

Is it possible to detect microvolt level TWA?

In order to detect non-visible TWA, novel signal processing techniques have been used: Fast Fourier transformation analysis[11], complex demodulation[8,12], autocorrelation method[13], and autoregression technique[14]. A commercial instrument that can identify microscopic TWA has approved by FDA as a non-invasive screening test to evaluate patients at risk for SCD.

TWA, visible or at microvolt level, occurs consistently in association with arrhythmias under diverse conditions, including coronary artery occlusion and release-reperfusion[8,15], variant angina pectoris[7], dilated[16], and hypertrophic cardiomyopathy[17], prior myocardial infarction[18,19], and in patients with the long QT syndromes[14]. Some investigators have shown the TWA as a marker of ventricular tachyarrhythmias and sudden cardiac death despite in the absence of acute myocardial ischemia[9,16]. Clinical results, presented at the 2002 annual meeting of the American Heart Association, demonstrate that Microvolt T-Wave Alternans (MTWA) testing can help determine which MADIT II type patients (prior myocardial infarction and left ventricular ejection fraction of 30% or less) should receive an implantable cardioverter defibrillator (ICD).

TWA analysis appears to be a promising new method with very high sensitivity and reasonable good positive

predictive value to risk-stratify patients for future arrhythmic events.
Although very important developments have been made in detecting TWA, there are many aspects that need further investigation. There are some problems encountered during analysis of the data; phase reversals in TWA magnitude, QT length changes due to variable heart rate, amplitude changes of TWA time series, and the effects of EMG interference on the performance of the analysis. Thus, the algorithms for investigating the TWA should be examined carefully considering the mentioned problems so that the optimal method of analysis could be found. Also there is the problem of missing data, which is due to abnormalities in the ECG signal and lead disconnections during data acquisition.
On the other hand, recently the new techniques of repolarisation assessment from the T wave morphology of ECG were proposed to overcome shortcomings of other noninvasive tools, such as the QT dispersion, to identify the patients with increased risk of sudden cardiac death. The total cosine R-to-T (TCRT), T wave morphology dispersion, T wave loop dispersion, normalised T wave loop area, T wave residuum evaluating non-dipolar ECG signal contents investigated as the new T wave morphology variables[20]. The TCRT, which is measuring the three-dimensional angle between the QRS and the T wave vector loop, and T wave loop dispersion have been found independent predictors of mortality in post MI patients. Independent prognostic value for the relative T wave residuum as well as the absolute T wave residuum was showed in a study including 813 male with cardiovascular disease[21]. The new T wave morphology variables appear to be promising new tools to risk-stratify patients for future arrhythmic events. However, more data are needed to establish their definite role in patient, susceptible to major cardiac arrhythmias.

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BC-05

ELECTROMECHANICAL RESPONSE TO ISCHAEMIA IN PATIENTS WITH CORONARY ARTERY DISEASE

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Ischaemia of an organ is the result of its blood supply being compromised to an extent that interferes with its function. The effects of myocardial ischaemia have been studied in detail over the last 70-80 years. The most obvious, which follows experimental occlusion of a major coronary artery is loss of contractile function. This leads to systolic wall thinning and outward endocardial motion of the affected region. Early observations of less severe ischaemia in angina pectoris demonstrated that the earliest abnormality was an increase in ventricular end-diastolic pressure, which preceded ST segment shift or the onset of symptoms. From this it was deduced that diastolic mechanisms were more sensitive to the effects of ischaemia than those of systole. More detailed experimental and clinical studies of regional function demonstrated an additional component of the ischaemic response: local asynchrony. This incoordination manifested itself as delay in the onset of regional wall motion with respect to that of the cavity as a whole[1], while the duration of local contraction itself remained largely unaltered. This implies that in affected areas, local contraction continues after aortic valve closure into the period of isovolumic relaxation. Such post-ejection shortening has come to be recognised as a sensitive marker of local ischaemia.

This incoordination has several important effects. It reduces the proportion of local myocardial work that is translated into useful work on the circulation, both in affected areas and elsewhere in the ventricle, thus impairing overall systolic function. The extent of this effect is large, accounting for 40% or more of local work. Incoordination during isovolumic relaxation reduces the rate of fall of left ventricular pressure, which itself impairs early diastolic filling, so that diastolic function is also compromised. Clearly, therefore, it is important to understand the basis of this asynergy. Theoretically the onset of myocardial shortening might be delayed because local tension development is impaired in the face of rising ventricular pressure supported by normal function elsewhere in the ventricle. However, this would not explain the otherwise normal duration of tension development. The possibility that local delay in the onset of contraction might be the result of delay in local activation, although briefly suggested some 25 years ago [1] has not been investigated in any detail until recently. Indeed, it is generally considered that ventricular activation is not acutely affected by ischaemia, and that QRS broadening represents the irreversible results of fibrosis. While standard exercise does not lend itself to recording ECG's of high technical quality, this is possible during dobutamine stress. The results of such a study demonstrated clearly that narrowing of the QRS complex by 5-10 ms is part of the normal response to stress, and that failure to do so lies outside the 95% confidence limits of normal. In patients with coronary artery disease, the development of ischaemia is associated with QRS broadening of 10-15 ms or more. These effects are very reproducible. Clearly, therefore acute changes in QRS duration are possible and the occurrence with stress is a criterion of normality.

Changes in QRS duration may be a simple paraphenomenon of stress, being independent of well recognised mechanical events. However, before this explanation can be accepted, the alternative hypothesis: that they form an integral part of the myocardial response to ischaemia must be rejected. In order to investigate this possibility, we studied left ventricular long axis function by echocardiography during dobutamine stress. In normal subjects, the onset of shortening occurs earlier, with respect to the Q wave of the ECG with stress. In individual subjects, the extent of this time change correlates closely with the extent of QRS shortening. In patients with coronary artery disease, the onset of long axis shortening is delayed as QRS broadens, and again the two are closely correlated in individual patients. Furthermore, the duration of both isovolumic periods is increased as long axis function becomes incoordinate, to an extent that also correlates with QRS change. This applies whether or not left bundle branch block is present and whether or not the ventricular cavity is dilated. It follows, therefore, that far from being a paraphenomenon, acute changes in QRS duration and associated mechanical changes are an important component of the myocardial response to acute ischaemia[2].

These results have practical consequences. Unlike ejection fraction or inotropic state, changes in total isovolumic time, when the ventricle is neither ejecting nor filling, are a major determinant of peak cardiac output during stress

in patients with left ventricular disease. A change in QRS duration of 5 ms causes total isovolumic time to alter by 3.5 s/min, which in turn alters peak cardiac output by 1.3 l/min[3]. It is of interest that similar changes occur with resynchronisation by atrio-biventricular pacing. These electromechanical changes account for what has previously been described as "impaired diastolic function". They have also proved very sensitive in detecting the presence or absence of coronary artery disease, even in patients with cavity dilatation or left bundle branch block. Their performance during dobutamine stress echocardiography is much superior to standard wall motion analysis. Finally, recognition that electrical as well as mechanical effects are involved in the response to ischaemia opens the way to pharmacological or even electrical manipulation, suggesting novel ways of treating symptomatic patients with coronary artery disease.

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BC-06

LEFT ATRIAL FUNCTION IN INTERATRIAL BLOCK (IAB)

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IAB (p-wave≥120ms) implies left artial (LA) enlargement (LAE), dysfunction, decreased ventricular filling, LA appendage thrombosis; it predicts atrial fibrillation and flutter. We determined the effects of IAB on LA function in patients with (24) and without (16) IAB matched for LA size, utilizing a Hewlett-Packert Sonos 5.500 imaging system with a 2.6-MHz transducer for transthoracic M-mode, 2 dimensional and Doppler echocardiography. Recordings: parastemal long axis, apical 4 chamber and 2 chamber and subcostal. Echocardiograms were analyzed for LA areas utilizing the spatial biplane area-length method at mitral opening, P-wave onset and mitral closure in apical 4- and 2- chamber views. Areas were measured by outlining the endocardium at specific freeze frames with a digitized graphic ball. Lengths were measured as the longest line between posterior LA wall and mitral midportion. Peak A-wave velocity and A-wave acceleration times were also measured. Measurements were taken offline from 3 consecutive cardiac cycles and averaged for: maximal LA volumes (Vmax), minimal LA volumes (Vmin), LA volume at onset atrial systole (Va), LA passive emptying volume (LAPV), LA stroke volume (LASV), LA total emptying volume (LAtv)- LA passive emptying fraction (LAPEF), LA EF, LA total emptying fraction (LATEF) and LA kinetic energy (LAKE) (Table).

LA Measurements and calculations*

	IAB	CONTROLS	p
AT	115±39 ms	83±24 ms	<0.01
LASV	7±5 ml	17±6 ml	<0.01
LAEF	9±6%	25±8%	<0.01
LAKE[1]	20±14	65±44 Kdyne/cm/s	<0.01

** Abbreviations: see text*

[1] LAKE varied inversely with p duration (r=0.51, p<0.01)

Conclusions: P-wave duration is an independent predictor of LAEF because both LAKE and LAEF correlated inversely with P-wave duration. Degree of dysfunction varied directly with the electrical delay due to IAB. Patients with IAB have poorly contractile LAs indicated by higher AT and lower LAEF and LAKE than do patients with comparable sized atrium but without IAB. Thus, delayed LA activation worsens LA systolic indices over and above that resulting from the mechanical effect of LAE alone. IAB is a marker of an electromechanically dysfunctional LA. IAB, LAE and LA dysfunction can be considered manifestations of an LA myopathy.

BC-07

RIGHT VENTRICULAR DYSFUNCTION

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Assessment of right ventricular function is more difficult than that of left ventricle. Unlike the left ventricle, asymmetrical complex geometry of the right ventricle precludes the use of geometric models for an accurate measurement of volumes . In addition the right ventricle contains separate anatomic regions (sinus, apical trabecular and infundibulum) that contract asynchronously under normal physiologic circumstances and these contractile patterns may be modified differently in conditions of right ventricle pressure or volume overload. Furthermore, difficulty in tracing the heavily trabeculated right ventricular endocardial border in end-systole also imposes a challenge to assess right ventricular volumes and function by the standard two-dimensional echocardiography.

Bearing these limitations in mind, echocardiography is nevertheless a very useful non-invasive technique for assessing right ventricular size and function. Instead of trying to measure volumes, the simpler measurements are justified . All Doppler measurements are subject to change with respiration. Measurements should be made during held end-expiration or by taking averaged values from a respiratory cycle.

Measurement of the right ventricular size can be made with M-mode echocardiography from left parasternal window in the long axis view at end-expiration.An internal diameter greater than 26 mm shows dilatation[1]. However there is no single M-mode measurement of right ventricular dimension that adequately shows its overall size. With two-dimensional echocardiography numerous right ventricular measurements of the ventricular inflow and outflow dimensions from apical 4-chamber and parasternal short axis sections must be made to be used in follow-up evaluations. The short axis parasternal view reveals the normal crescent-shaped cross-section of the right ventricle and is very useful for the assessment of septal motion.Both volume and pressure overload of the right ventricle results in a ventricular septal motion abnormality[2]. In volume overload there is dilatation of the right ventricle and diastolic flattening of the ventricular septum . In diastole, due to the high right ventricular end-diastolic volume and pressure, diastolic displacement of the septum towards the left ventricle occurs and the left ventricle takes a "D"-shaped configuration rather than circular geometry. The degree of septal displacement correlates with end-diastolic trans-septal gradient.At the onset of systole with restoration of the normal transseptal systolic pressure gradient the septum is shifted towards the normal orientation and the left ventricle becomes circular in early systole.This rearrangement of ventricular shape pushes the septum into the right ventricular cavity (paradoxical septal motion) and might contribute to right ventricular ejection. In right ventricular pressure overload septal motion decreases initially, with further increase in pressure there is flattening of the septum not only in diastole but in systole as well.With marked increase in right ventricle systolic pressure right ventricle becomes more circular leading to a concave septal configuration in end-systole. This paradoxical septal motion implies that in such high right ventricular pressure overload cases septum contributes to right ventricular ejection rather than to left ventricle's . The outflow tract can also be imaged in a short axis view at a slightly higher level. From the apical 4-chamber view an overall estimate of the cavity dimension is made. The subcostal window is also very useful. In patients with chronic obstructive lung disease, the subcostal approach often represents the only available transthoracic window. Regional systolic function of the right ventricular free wall can be assessed by evaluating wall thickening as normal, hyperkinetic, hypokinetic and akinetic. The thickness of the right ventricular wall is best measured by M-mode. Wall thickness over 5 mm indicates right ventricular hypertrophy[1].

A simplified assessment of the right ventricular long axis function can be made by measuring the systolic excursion of the tricuspid annulus in the apical 4-chamber view by M-mode echocardiography[3,4].The difference between end-diastolic and end-systolic measurement is an index of right ventricular global systolic function. The deeper layers of the right ventricular myocardium are arranged longitudinally, the apex is fixed and since the rotation about the long axis is minimal this technique is appropriate for measurement of inflow shortening. M-mode recording of this motion has been found to correlate well with radionuclide right ventricular ejection fraction . Tricuspid annular velocity measured by tissue Doppler PW at the free wall is another and new way of assessing the right ventricular function in the long axis[5,6]. Since pulsed Doppler tissue echocardiography measures myocardial velocity rather than atrio-ventricular ring movement and velocity reflects long axis shortening it is very appropriate for the rapid, noninvasive evaluation of right ventricular systolic function. A good correlation has been found between tricuspid systolic annular

velocity and right ventricular ejection fraction. A systolic annular velocity < 11.5 cm/s predicts right ventricular dysfunction with a sensitivity of 90% and a specificity of 85%[7].

Color kinesis which color encodes endocardial motion throughout the cardiac cycle has also been used for the quantitative evaluation of regional right ventricular systolic and diastolic function[8]. However, the value of this technique for the objective assessment of regional right ventricular function has yet to be determined. Recently, myocardial acceleration during isovolumic contraction has been proposed as an index of right ventricular contractility[9]. Isovolumic myocardial accerelaration 'IVA' measured by tissue Doppler describes the rate of change of contractile force during isovolumic contraction and thus unaffected by loading conditions and should prove useful in the assessment of right ventricular function.

The estimation of pulmonary artery systolic pressure is made using the velocity of the tricuspid regurgitant jet to obtain right ventricular to right atrium pressure gradient. To this an estimate of right atrial pressure is added. The best method for estimating the right atrial pressure is assessment of the size and dynamics of the inferior vena cava. Measurement of the inferior vena cava diameter adjacent to the right atrium in the subcostal view and checking the diameter change with respiration will determine what to add to gradient in the formula. A tricuspid regurgitant jet suitable for measurement can be found in more than 90% of patients. In the absence of tricuspid regurgitation, mean pulmonary artery pressure can be calculated from the time to peak velocity in the pulmonary outflow tract which is called the acceleration time. Pulmonary acceleration time over 120 ms is usually normal. The use of E/A ratio, in combination with E-wave deceleration time has been used as a qualitative measure of diastolic function of the right ventricle. However, the diastolic properties of the right ventricle are very different from those of left ventricle. Unlike the left ventricle ,the right ventricle is not a closed system in diastole The low pulmonary artery end diastolic pressure associated with a low pulmonary vascular resistance can easily be overcome by right atrial systolic pressure under some circumstances. In restrictive right ventricular disease in late diastole the right ventricle may be acting as a conduit between the right atrium and pulmonary artery. With premature opening of the pulmonary valve, there will be an antegrade diastolic flow into the pulmonary artery with atrial systole. As a result real changes in myocardial compliance may not be reflected by trans-tricuspid flow velecities. Late diastolic pulmonary arterial laminar flow with atrial systole , throughout the respiratory cycle is considered the hallmark of restrictive right ventricular physiology[10]. Also, in the presence of restrictive disease hepatic vein Doppler examination will display reduced systolic velocity and increased diastolic velocity, the small amount of retrograde flow normally present will be amplified and the tricuspid E-wave deceleration will be shorter. Three-dimensional echocardiography is still investigational for right ventricular volume measurements.

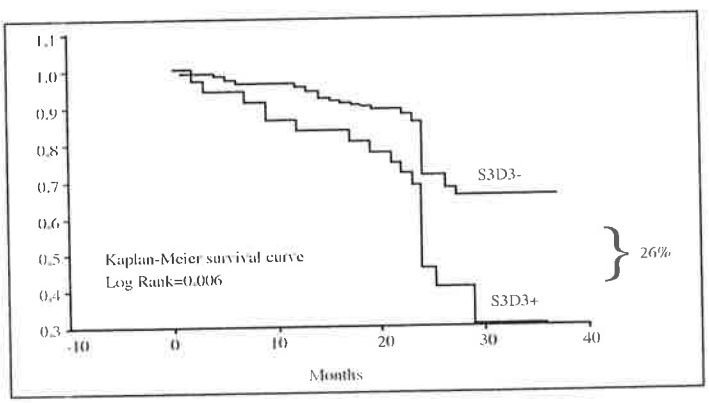

Figure 1: Kaplan-Meier survival curve showed a significant 26% increase of total mortality in patients with SF3-D3 compared to those without SF3-D3 (Log Rank= 0.006) during a follow-up

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BC-08

RESTRICTIVE PATTERN AS A PROGNOSTIC MARKER OF SEVERITY IN PATIENTS WITH CONGESTIVE HEART FAILURE

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Patients with severe LV systolic dysfunction and congestive heart failure have a very poor prognosis and frequent hospital re-admissions. However, once severe LV dysfunction is established, further prognostic differentiation is difficult. In the past decade many studies have demostrated that restrictive filling pattern consistently and independently predicted cardiac mortality better than LV ejection fraction[1,2]. In another study three types of diastolic pattern (impaired relaxation, pseudonormal and restrictive) were compared during one-year follow-up[3]. Incremental increase of all-cause mortality and hospital readmissions were observed in patients with impaired relaxation, pseudonormal and restrictive diastolic transmitral pattern, respectively.

However, no data exist comparing the impact of the combined presence of both poor LV systolic function (EF< 40%) and restrictive transmitral patter on cardiac mortality during the follow-up[4]. In our study, 306 consecutive patients (120 males, 186 females, mean age 72±10y) hospitalised for CHF NYHA class II-IV were prospectively studied from January 1996 to January 2000. All pts during the hospitalisation underwent clinical, laboratory, and routine chest X-ray examinations as well as complete echocardiographic examination. Univariate and multivariate analysis and Kaplan-Meier curves were performed to test the association between LV systolic and diastolic dysfunction and cardiac mortality and morbidity in a follow-up of 23.7±7.2 months. The etiology of CHF was CAD in 67%, HTN in 72%, DM in 50%, stroke in 12%, valvular heart disease in 5% and other in 21% of pts. Advanced NYHA III and IV class was present in 31% and 18%, respectively. 99 (32%) pts had normal LV systolic function (S1), 123 (40%) patients had LV EF less than 30% (S3) and 36 (12%) pts had both poor LV systolic function and restrictive diastolic filling (S3D3). In univariate analysis, 2-year mortality was highest in S3D3 group (55%) and was significantly higher compared with those in S1 (29%) and S3 (38%, p = 0.001). Hospital admissions were significantly higher in S3 (53%) compared with S1 group (36%, p=0.005) in a 2-year folow-up (Table 1). Using the Kaplan-Meier survival curve model, a 33% increase of cardiac mortality in S3D3 compared to S1 group (Log Rank=0.004) and a 26% increase of cardiac mortality in S3D3 compared to the non-S3D3 group (Log Rank=0.007) (Figure 1) were observed. In multivariate Cox proportional-hazard analysis, S3D3 group (p=0.0001, OR 2.43, 95% CI 1.39-4.23), age (p=0.00001, OR 1.07, 95% CI 1.04-1.103), increased serum creatinine (p=0.03, OR 3.18, 95% CI 1.09-2.92) and atrial fibrillation (p=0.039, OR 1.56, 95% CI 1.02-2.37) were associated with increased cardiac mortality in the 2-year follow-up. In conclusion, the simultaneous finding of both poor LV systolic function and restrictive LV filling pattern identified a subgroup of patients with highest 2-year cardiac mortality. Those findings are more predictive for increased cardiac mortality if present simultaneously, compared to those with poor LV systolic dysfunction alone.

Table 1: The effect of LV systolic and diastolic function on 1- and 2- year mortality and hospitalisations

PARAMETER	**SF1** (EF≥55%) n=99	**SF1** (EF≥40%) n=123	**SF3-D3** (EF≤40%+restrictive FP) n=36
1-year mortality	4(4%)*	16(13%)*	6(17%)*
2-year mortality	29(29%)**	47(38%)**	20(55%)**
1-year hospitalisations	25(25%)	40(33%)	15(42%)
2-year hospitalisations	36(36%)*	65(53%)*	17(47%)

**p=0.05, **p=0.00*

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Myocardial Viability

BC-09

VIABILITY ASSESSMENT AND ECHOCARDIOGRAPHY

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Left ventricular systolic dysfunction is the final stage of most cardiovascular diseases. It manifests itself as heart failure (HF) and, heart failure is associated with poor morbidity and mortality. The severity of the clinical picture of HF is directly related to the prognosis of HF. The major cause of HF and chronic left ventricular dysfunction is coronary artery disease. Despite the trend of decreasing death rates due to both ischemic heart disease and stroke, HF prevalence and resultant death rates is increasing[1].

During the last 20 to 25 years our understanding about the relationship between myocardial perfusion and left ventricular function has changed considerably with the introduction of stunned and hibernating myocardium[2,3]. Severe reduction of coronary blood flow more than 20-40 minutes causes cell death, myocardial necrosis begins to develop and contractile function is lost irreversibly. If the ischemia is transient and followed by reperfusion, transient regional dysfunction which is termed stunned myocardium develops. This contractile dysfunction is thought to be caused both by ischemia and reperfusion injury. Interventions aimed at reducing the number, severity or the duration of ischemic episodes improve the contractile function[2]. On the other hand, myocardial hibernation seems to be an adaptive process rather than an injurious response. Viable but hypocontractile myocard results from prolonged myocardial hypoperfusion. Interventions altering the supply -demand relationship of the myocardium favorably may result in improvement of contractility in hibernating myocardium[3]. In patients with coronary artery disease occurrence of pure stunning or hibernation is infrequent and both states coexist.

Since both the stunned and the hibernating myocardium can be altered by interventions, identification of these states is clinically very important. Furthermore, akinetic myocardium without entirely necrotic or fibrotic myocardium may, also, be found in patients with nontransmural myocardial infarction and during a short period of reversible ischemia. Identification of these different myocardial states is diffucult and may require more than one technique. Various methods are available for the assessment of viability. Nuclear techniques evaluating myocardial cell membrane integrity , and cellular metabolic processes like single photon emission tomography (SPECT) and positron emission tomography (PET) can be used. Magnetic resonance imaging (MRI) is a new and promising method to evaluate myocardial viability. Myocardial contractile reserve can be evaluated by echocardiography.

The most frequently used echocardiographic test of myocardial viability is dobutamine stress echocardiography (DSE). Dipyridamole is an alternative stressor that can be used.

Dobutamine is asynthetic catecholamine with positive inotropic effects mediated predominantly through 1 adrenergic stimulation. Dobutamine has positive inotropic action at low doses (4-8g/kg / min.) and increase heart rate only at doses above 10 g/kg/min. In low dose DSE, dobutamine infusion is started with 5 g/kg/min and increased up to 10 or 20 g/kg/min in every 3 minutes in steps (5,10 and 20). Another alternative protocole is the high dose DSE protocole. It begins with 5 g/kg/min dobutamine infusion, with increases in dose every 3 minutes in steps 10,20,30, 40 g/kg/min with the addition of atropine (0.25-1.0 mg) until a test endpoint is reached. Test endpoints are the detection of new wall motion or the occurrence of complications. During low dose phase, improvement in segmental wall motion has to be carefully monitered, if possible using side-by-side simultaneous quad screen technique in order to detect viability before heart

rate increases. Viability is defined as an improvement in wall motion score 1 in >1 segment. Apart from viability new wall motion abnormalities (ischemia) and segments with improvement in wall motion followed by worsening (biphasic response) can be detected. Scar tissue is diagnosed in akinetic segments without any wall motion improvement. (Figure 1). According to the guidelines both DSE and dipryidmole SE is a class I indication for the diagnosis of coronary artery disease (CAD) and for the prognostic stratification of patients with known CAD[4,5].

Low-dose DSE has been found to have a sensitivity ranging from 66% to 86%, with specifities ranging from 68% to 94% for detecting regional recovery after myocardial infarction[6]. The overall positive and negative predictive values were 71% and 87%, respectively. The contractile response of the asynergic myocardium to low-dose DSE was found to be highly predictive of postrevascularization recovery of function (positive predictive value 82% to 100 %)[6]. The use of higher doses of dobutamine led to improvement in the sensitivity of DSE for detection of viable myocardium and in addition patients with biphasic response (recovery of contarctile function at low doses and deterioration with high doses) were identified . This biphasic response was found to be highly predictive of functional recovery after revascularization (overall sensitivity and spesificity 69% and 87%)[7].

Prognostic value of pharmacological (Dobutamine or dipryidamole) SE in patients with known or suspected has been recently addressed in a large-scale multicenter prospective study[8]. In this study, 7333 patients were followed for a mean of 2.6±3 years after DSE. The cardiac mortality rate was 2.1% for the whole group. There was a significant difference between the test negative and positive groups (1.81% vs. 2.8% , p=0.0046). Age, previous Q and non-Q wave myocardial infarction and peak wall motion score index were independent predictors of cardiac death. The absence of contractile reserve to low-dose dobutamine in patients with coronary artery disease and severe symptomatic left ventricular systolic dysfunction has been found to be a potent predictor of 3 year mortality[9]. The presence of contractile reserve and ischemia (biphasic response) predicts a high risk of cardiac events and mortality[10,11]. Surgical treatment in patients with viability leads to a better mortality rates when compared with medically treated patients (3% vs15%, p< 0.01)[12]. In the absence of contarctile reserve mortality was high irrespective of the treatment strategy (22% medical treatment vs %28 % surgical treatment, p=NS)[12]. The accuracy of DSE in detecting myocardial viability is comparable with the data on nuclear perfusion imaging and PET studies. Spect and PET seems to have higher sensitivities compared with DSE, but DSE seems to be more spesific. These differences reflect underlying alterations in cellular metabolism and function. Blood flow and flow reserve may be reduced to such an extent that contractile reserve is lost while transmembrane pump function is preserved. Spect or PET can detect small regions of viable myocardium which are unable to permit improvement in systolic function. Histological evaluation of the explanted hearts after transpalntation suggested that contactile reserve as evidenced by positive DSE requires at least 50% viable myocytes in a given segment[13]. It is now clear that a substantial proportion of dysfunctional segments in patients with chronic ischemic heart disease is comprised of viable tissue, with a potential for functional recovery following revascularization. Detection of viable myocardium in these patients favorably affects the prognosis and the choice of therapy. DSE seems to be a safe and reliable noninvasive method for detection of viability.

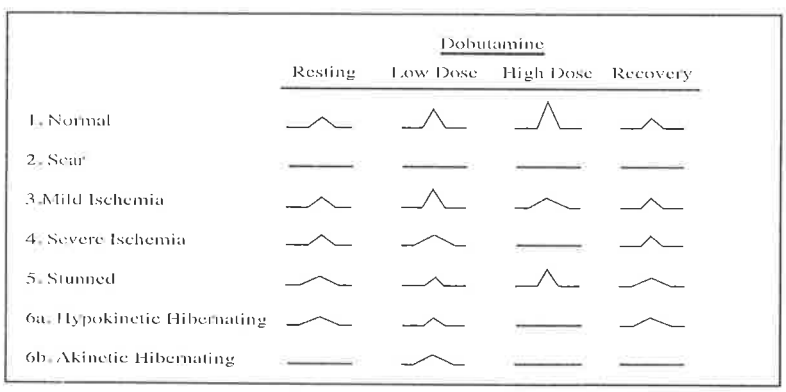

Figure 1: *Diagram showing various patterns of segmental contractile response to inotropic stimulation during dobutamine stress echocardiography (DSE).*

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BC-10

MYOCARDIAL PERFUSION SCINTIGRAPHY IN THE DETECTION OF MYOCARDIAL VIABILITY

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It has been proven that impaired left ventricular function is not always an irreversible process, and may improve after myocardial revascularization[1-4]. On the other hand, revascularization carries a higher risk in patients with severely depressed left ventricular function[5]. Therefore the assessment of myocardial viability is of paramount importance in patients with chronic ischemic heart disease and left ventricular dysfunction. Several methods have been developed for the viability assessment[6].

Rationale for the methods used for the identification of viable myocardium:

1. To demonstrate functional integrity: Dobutamine stress echocardiography, MRI
2. To demonstrate cellular membrane integrity: Perfusion imaging, PET imaging.
3. To demonstrate metabolic integrity: PET imaging, FDG-SPECT

Perfusion Imaging in Viability Assessment:

Conventional radiotracers used for the identification of viable myocardium include Tl-201 and Tc-99m-labeled perfusion agents. Sestamibi is the most commonly used Tc-99m labelled perfusion tracer. Planar or SPECT thallium-201 imaging is the most common perfusion imaging in viability assessment. After IV injection, initial uptake of Tl-201 is proportional to regional myocardial blood flow. Perfusion defects detected after exercise on the Tl-201 images indicate transient ischemia, scar or the combination of both. Redistribution after 4 hours reflects the integrity of cellular membrane. Complete redistribution indicates ischemia, and partial redistribution reflects viable myocardium. Persistent Tl-201 defects indicate myocardial scar. But some persistent thallium defects do not represent irreversibly injured myocardium, and improvement in regional wall motion can be shown after revascularization[7,8].

Several protocols have been employed for viability assessment with Tl-201:

1. Stress- 4 hours redistribution images
2. Stress- 4 hours redistribution, delayed (24 hours) images

3. Stress- redistribution and reinjection images
4. Stress- immediate reinjection, delayed images
5. Rest- 4 hour delayed redistribution imaging

Predictors of viability on thallium imaging are as follows:

1. Normal initial Tl-201 uptake
2. Tl-201 uptake > 50% of that of normal region
3. Delayed (4 hours) redistribution
4. Late (24 hours) redistribution
5. Enhanced thallium uptake after reinjection

Reinjection technique which is described by Dilsizian and Bonow[9] consists of the administration of a second dose of thallium after the acquisition of redistribution images is one of the commonly used protocols. Rest-redistribution protocol is accepted most useful in viability assessment by Beller[4]. In a review, positive predictive accuracy of rest-redistribution-reinjection thallium imaging in prediction of functional improvement after revascularization is reported as 69%, and negative predictive accuracy as 89%[6]. In this review, analysis of four studies of SPECT rest-redistribution imaging, comparable positive and negative predictive accuracies (69% and 92%, respectively) is found. Tc-99m sestamibi is the second commonly used perfusion agent in detecting myocardial viability. Myocardial uptake of Tc-99m sestamibi is proportional to regional perfusion and, it depends on the cellular membrane integrity, and may therefore, reflects viability. Studies comparing the Tc-99m sestamibi SPECT to Tl-201 SPECT showed concordance between two imaging modalities[10,11]. Sensitivity and spesificity of sestamibi SPECT in detecting functional recovery after revascularization was found 94% and 86%, respectively[10]. Because of physical properties of Tc-99m and sestamibi, ECG gated perfusion images can be easily acquired with sestamibi. Gating allows for simultaneous assessment of myocardial perfusion during stress, and resting regional systolic function at rest[12].

Sestamibi SPECT parameters in the assessment of myocardial viability are as follows:

a.. Normal uptake after stress or rest
b. Mildly decreased uptake (>50% of normal region) at rest
c. Reversible defects
d. Preserved systolic function on gated imaging

It is also shown that, nitroglycerin administration prior to either sestamibi or thallium injection may further improve detection of myocardial viability[8].

Newer Imaging Modalities:

Tc-99m labeled hypoxia agents have been studied as new markers of myocardial viability[13]. Studies with two radiolabelled-fatty acids; I-123 iodophenyl penta adecanoic acid (IPPA) , and I-123 beta methyl iodophenyl penta adecanoic acid (BMIPP) suggested they may be useful in detecting viable myocardium[14-16]. FDG imaging, conventionally used for metabolic imaging with PET, can now be undertaken with SPECT camera and a 511-keV collimator or without collimation (coincidaence imaging)[17].

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Atrial Fibrillation

BC-11

CONVERSION OF ACUTE ATTACK

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One of the first questions that must be addressed when a patient presents with atrial fibrillation (AF) is the duration of the episode. Episode duration is of considerable importance for three reasons. First, many of initial episodes of AF will terminate spontaneously within the first 12 to 24 hours. Second, the longer duration of the episode, the more likely it will be resistant chemical or electrical cardioversion. Third, prolonged episodes (> 48 hours) of AF are associated with a clinically important risk of embolic events after chemical or electrical cardioversion. Episodes of < 48 hours duration, should be evaluated according to the stability of patient in terms of severe ischemia, hypotension or heart failure. These clinical situations may indicate the emergency cardioversion of AF. Emergency direct current cardioversion should be performed with appropriate sedation and with an initial energy of 200 Joules with synchronization of direct current. Ventricular rate control should be the first therapeutic step in the majority of patients with acute episode of AF when the patient is hemodynamically stable. Patients who present with new AF (less than 48 hours) frequently convert back to normal sinus rhythm spontaneously within the first 24 hours, in many as 70-80 % of cases. Pharmacological interventions with some antiarrhythmic drugs facilitate to return to the sinus rhythm as much as early. Oral or intravenous administration of flecainide and propafenone has been reported to result in high rate of cardioversion when compared to placebo in majority of patients if AF is of less than 48 hours. Despite a few small series have reported the use of intravenous amiodarone administration for a acute termination of paroxysmal AF, in controlled trials amiodarone was found to be only marginally better than placebo. Episodes of > 48 hours duration, should be immediately managed similar to that of patients with AF of less than 48 hours duration. If the patient does not require emergent direct current cardioversion, ventricular rate control should be the first step. Appropriate anticoagulation and more resistance of pharmacological cardioversion are different issues in patients with AF longer than 48 hours. Ibutilide, a newly released antiarrhythmic agent, has shown high efficacy in clinical trials for the conversion of chronic AF to sinus ryhthm.
A number of antiarryhthmic drugs may be used for the pharmacological cardioversion of AF. Unfortunately, studies in the literature are difficult to compare as they often include patients with varying durations of AF, a major determinant of conversion rate.

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RATE CONTROL VS RHYTHM MANAGEMENT IN PATIENTS WITH ATRIAL FIBRILLATION: LESSONS FROM NEW TRIALS

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Atrial fibrillation (AF) is the most common sustained cardiac disturbance. The incidence of AF increases markedly with age. The main symptoms are palpitation, breathlessness, and dizziness, and AF may lead to congestive heart failure. The disorder is an important risk factor for stroke. The preferred and most frequently used initial therapy for AF is a strategy to restore and maintain a normal heart rhythm[1,2].
Stroke prevention is a key component of therapy for AF, and both rate control and rhythm control therapy strategies also use an anticoagulant drug to prevent embolic complications.
In AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial, 4060 patients with AF at least together with one risk factor (age≥65, diabetes mellitus, hypertension, and congestive heart failure) were randomly assigned to a rate control and rhythm control treatment strategy and were followed for an average of 3.5 years[3]. Both groups also treated with warfarin. Digoxin, beta blockers or calcium channel blockers were used for rate control, and amiodarone, sotalol, propafenone, procainamide, quinidine, flecainide, disopyramide or moricizine was used for rhythm control. There was no difference observed when both strokes and deaths and other major events were considered together. Adverse drug effects were more common in the rhythm control group. Patients in rhythm control group were more likely to be hospitalized. Drugs used to control heart rate are usually less expensive. The findings of AFFIRM study may not apply to every patient, particularly younger patients or those without risk factors.
In RACE study including 522 patients with persistent AF, there is no difference in the composite endpoint (cardiovascular death, heart failure hospitalization, thromboembolic complications, severe bleeding, pacemaker implantation, and severe adverse effects) between the two strategies[4].
The mainstay of managing AF is drug therapy. In the minority of patients in whom AF can not be adequately managed by pharmacological therapy, the most appropriate type of nonpharmacological therapy (atrial pacing, implantable atrial defibrillator, AV junction ablation, AV node modification, focal ablation within pulmonary veins, pulmonary vein isolation, segmental isolation of pulmonary veins, linear catheter ablation, surgical Maze operation, catheter ablation during cardiac operation) must be selected on an individualized basis. For example, biatrial pacing may be most appropriate choice in a patient with sick sinus syndrome. The segmental isolation of pulmonary veins may be the most attractive option in a young patient with very symptomatic and frequent attacks of AF. On the other hand, the most appropriate approach for an old patient with chronic AF may be rate control by drug therapy to minimize symptoms and prevent tachycardia-induced cardiomyopathy.

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BC-13

ELECTROMECHANICAL RESPONSE TO ISCHAEMIA IN PATIENTS WITH CORONARY ARTERY DISEASE

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Ischaemia of an organ is the result of its blood supply being compromised to an extent that interferes with its function. The effects of myocardial ischaemia have been studied in detail over the last 70-80 years. The most obvious, which

follows experimental occlusion of a major coronary artery is loss of contractile function. This leads to systolic wall thinning and outward endocardial motion of the affected region. Early observations of less severe ischaemia in angina pectoris demonstrated that the earliest abnormality was an increase in ventricular end-diastolic pressure, which preceded ST segment shift or the onset of symptoms. From this it was deduced that diastolic mechanisms were more sensitive to the effects of ischaemia than those of systole. More detailed experimental and clinical studies of regional function demonstrated an additional component of the ischaemic response: local asynchrony. This incoordination manifested itself as delay in the onset of regional wall motion with respect to that of the cavity as a whole[1], while the duration of local contraction itself remained largely unaltered. This implies that in affected areas, local contraction continues after aortic valve closure into the period of isovolumic relaxation. Such post-ejection shortening has come to be recognised as a sensitive marker of local ischaemia.

This incoordination has several important effects. It reduces the proportion of local myocardial work that is translated into useful work on the circulation, both in affected areas and elsewhere in the ventricle, thus impairing overall systolic function. The extent of this effect is large, accounting for 40% or more of local work. Incoordination during isovolumic relaxation reduces the rate of fall of left ventricular pressure, which itself impairs early diastolic filling, so that diastolic function is also compromised. Clearly, therefore, it is important to understand the basis of this asynergy. Theoretically the onset of myocardial shortening might be delayed because local tension development is impaired in the face of rising ventricular pressure supported by normal function elsewhere in the ventricle. However, this would not explain the otherwise normal duration of tension development. The possibility that local delay in the onset of contraction might be the result of delay in local activation, although briefly suggested some 25 years ago [1] has not been investigated in any detail until recently. Indeed, it is generally considered that ventricular activation is not acutely affected by ischaemia, and that QRS broadening represents the irreversible results of fibrosis. While standard exercise does not lend itself to recording ECG's of high technical quality, this is possible during dobutamine stress. The results of such a study demonstrated clearly that narrowing of the QRS complex by 5-10 ms is part of the normal response to stress, and that failure to do so lies outside the 95% confidence limits of normal. In patients with coronary artery disease, the development of ischaemia is associated with QRS broadening of 10-15 ms or more. These effects are very reproducible. Clearly, therefore acute changes in QRS duration are possible and the occurrence with stress is a criterion of normality.

Changes in QRS duration may be a simple paraphenomenon of stress, being independent of well recognised mechanical events. However, before this explanation can be accepted, the alternative hypothesis: that they form an integral part of the myocardial response to ischaemia must be rejected. In order to investigate this possibility, we studied left ventricular long axis function by echocardiography during dobutamine stress. In normal subjects, the onset of shortening occurs earlier, with respect to the Q wave of the ECG with stress. In individual subjects, the extent of this time change correlates closely with the extent of QRS shortening. In patients with coronary artery disease, the onset of long axis shortening is delayed as QRS broadens, and again the two are closely correlated in individual patients. Furthermore, the duration of both isovolumic periods is increased as long axis function becomes incoordinate, to an extent that also correlates with QRS change. This applies whether or not left bundle branch block is present and whether or not the ventricular cavity is dilated. It follows, therefore, that far from being a paraphenomenon, acute changes in QRS duration and associated mechanical changes are an important component of the myocardial response to acute ischaemia[2].

These results have practical consequences. Unlike ejection fraction or inotropic state, changes in total isovolumic time, when the ventricle is neither ejecting nor filling, are a major determinant of peak cardiac output during stress in patients with left ventricular disease. A change in QRS duration of 5 ms causes total isovolumic time to alter by 3.5 s/min, which in turn alters peak cardiac output by 1.3 l/min[3]. It is of interest that similar changes occur with resynchronisation by atrio-biventricular pacing. These electromechanical changes account for what has previously been described as "impaired diastolic function". They have also proved very sensitive in detecting the presence or absence of coronary artery disease, even in patients with cavity dilatation or left bundle branch block. Their performance during dobutamine stress echocardiography is much superior to standard wall motion analysis. Finally, recognition that electrical as well as mechanical effects are involved in the response to ischaemia opens the way to pharmacological or even electrical manipulation, suggesting novel ways of treating symptomatic patients with coronary artery disease.

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AMBULATORY BLOOD PRESSURE MONITORING

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Introduction

Ambulatory blood pressure monitoring (ABPM) is a technique for measuring blood pressure over a period of 24 hours while subjects go about their normal daily activity. The patient wears a small monitor the size of a Walkman radio (similar in size to a Holter monitor system, but heavier, due to the battery power pack, which is carried on a waist belt), which takes readings automatically every 15 to 30 minutes and stores them in its memory. The main advantages of this technique are that it gives a more reliable and accurate measure of the blood pressure, for two reasons: first, a large number of readings are taken, and second they are taken outside the artificial environment of the doctor's office. This gives a better prediction of the risk associated with high blood pressure than the doctor's readings[1]. It is widely accepted that sleep/wake periods should be based on patients' actual sleep and wake times. The latter are often based on patients' diary information. However blood pressure (and continuous ECG recordings) provide more objective data and provide data on the circadian cycle: higher pressures during the day and lower pressures at night.

Also to evaluate the prevalence of hypertension and borderline hypertension (above the limit 140/90 mmHg according to the British Hypertension Society), the 24-h pressure profile and the efficacy of antihypertensive therapy, ABPM remains the method of choice.

Other applications include

1. nocturnal hypertension: the so-called non-dippers. In some patients the blood pressure does not show the usual 10% nocturnal fall during the night. There is evidence that these patients may be at higher risk of complications from their high blood pressure.
2. resistant hypertension: in some patients the blood pressure remains high, despite taking many different drugs (3 or more) to lower it. ABPM may show that the blood pressure is lowered outside of the doctor's office.
3. pregnancy: white coat hypertension occurs in about 30% of pregnant women, leading to unnecessary medication.
4. even too low blood pressure: in some young people (especially petite women) low blood pressure may cause symptoms of weakness and fatigue and may even lead to fainting.

Ambulatory blood pressure monitoring: methods

The development of non-invasive ABPM devices has added a new tool to clinical hypertension research. However development of clinically useful and widely accepted devices has been a technological challenge.

Figure 1: *Portable ABPM device for continuous readings up to 24 hours with finger cuff principle. After a certain duration, usually 10 minutes, the cuff pressure changes from finger.*

Devices based on different principles are available

- Auscultation: with an arm cuff and based on the detection of the onset and disappearance of Korotkoff sounds by a microphone placed over an artery distal to a deflating compression cuff. Another device uses ultrasound to detect disappearance of blood flow.
- Cuff oscillometry: which relies on the detection of cuff pressure oscillations. Systolic and diastolic pressures correspond to cuff pressures at which oscillations first increase (systolic) and cease to decrease (diastolic). The end points are approximated by analysis with different algorithm according to the manufactures, creating a potential source of variability (Accutracker II, Spacelab).
- Volumetric oscillometry: usually of a finger (Figure 1), with detection of volume pulsations under a cuff. Results are shown in Figure 2 (Portapres).

The two former methods are using arm cuffs. As these relatively large and bulky devices use quit some power for inflating the cuff, they only allow punctual readings every 15 to 30 min. In case of arm cuffs it is important that the inflatable bladder of the sphygmomanometer to encircle at least 80% of the arm and preferably the entire arm, this may be a problem especially in obese patients. The latter method on the other hand, due to its smaller size and less power consumption, allows continuous readings of blood pressure. An example of a continuous ABPM tracing is shown in Figure 2 (top), with the corresponding systogram (bottom) derived from the pressure tracing.

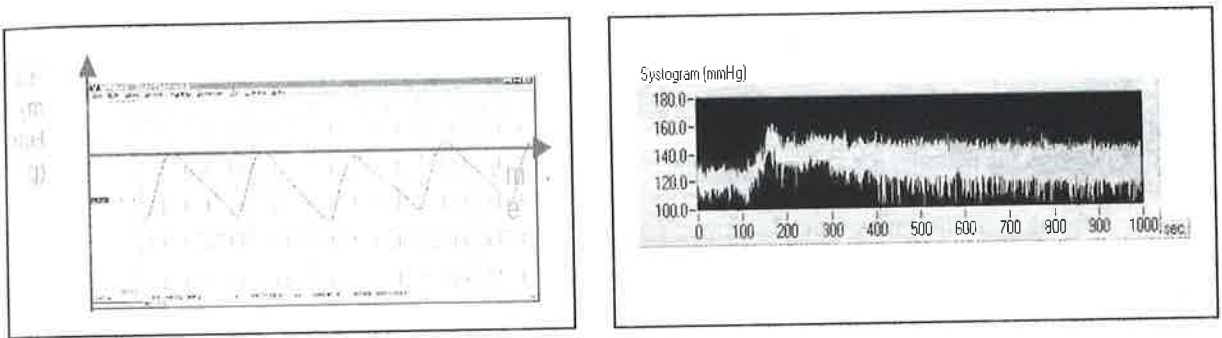

Figure 2: Upper tracing: short recording of blood pressure obtained from finger cuff device, lower tracing: corresponding systogram from a 15 minutes ABPM recording

Applications of ambulatory blood pressure monitoring

The importance of ABPM in managing hypertension has been widely acknowledged. More specific reasons to use ABPM can be summarised as follows[3]

- To exclude "white coat" hypertension.
- Follow-up of borderline hypertension.
- Study the effect on blood pressure of long duration physical exercising (endurance and power training)[4].
- ABPM may be a better predictor of cardiovascular events and mortality than clinical blood pressure readings.
- Control of patients with nocturnal high blood pressure.
- ABPM provides a 24 hour blood pressure profile, allowing assessment of clinic effects, drug effects, work influence, life style changes...

Conclusions

The rationale for the use of ABPM in clinical practice is evidence based. The technique is very specialised and should be reserved to experienced service providers. Physicians using ABPM should receive adequate training for using the devices: assessment and evaluation of the method and calibration testing. Patients should preferentially be monitored on a normal working day, rather than a rest day. It has been reported that ABPM data show a good reproducibility. Ideally an ABPM device should be combined with a continuous ECG monitoring (Holter monitor) system. A combination of the two has a lot to offer for clinical diagnosis purposes. Such a device is under development for space applications.

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BC-15

ECHOCARDIOGRAPHY IN LABORATORY ANIMALS

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Forty years after the introduction of echocardiography in clinical practice, the ultrasonic technology is now currently in laboratories for the evaluation of heart function and morphology in experimental research. The development of echocardiography to investigate small animals became crucial with the fast generation of transgenic mice and rats. These animals are studied regarding their heart morphology and function, identification of their phenotypes and/or to detect pharmaco-genetic interactions. Moreover animal models, currently used in pharmacology, such as experimental myocardial infarction, adriamycin-induced cardiomyopathy or hypertensive cardiomyopathy, especially in rats have brought out the necessity to adapt tools to these new conditions. The specifications required for these examinations are related with the small size of rats and mice, their physiology and specially tachycardia which in conscious rats is as high as 300 to 350 beats/min (bpm), reaching 500 bpm in conscious unstressed mice.

For that purpose, the material used in our laboratory is a Philips 5500 SONOS equipped with the 15L6 (15 MgHz) linear and the S12 (12 MgHz) sectorial probes. For both probes harmonic imaging is not available. Cardiac imaging is realised with special software settings to enlarge images. In normal mice the left ventricular cavity measures less than 4 mm in diastole and all the cardiac structures are visible in a depth of 1 cm. With this settings it was possible to examine our subjects in 2 D imaging at the rate of 100 to 250 Hz in some special condition (focusing on a area of interest), with the two probes.

Rats are examined in anaesthetized conditions, the heart rate being usually unaffected. In mice, the first line examination is performed in anaesthetized conditions to reduce the heart rate between 300 and 350 bpm. When required, this species can be studied in the conscious state after an training period.

Animals are studied in a classical way using 2D and M-mode examinations, the latter being specially useful to measure left ventricular dimensions. The parasternal 2D view allows good imaging of the left ventricle for the kinetics and of aorta. The left atrium is generally visible despite it's small size. This parasternal view permits Doppler recordings of the aortic and of the mitral flows with good quality tracings. M-mode as well as Doppler tracings are registered at 150 mm/s.

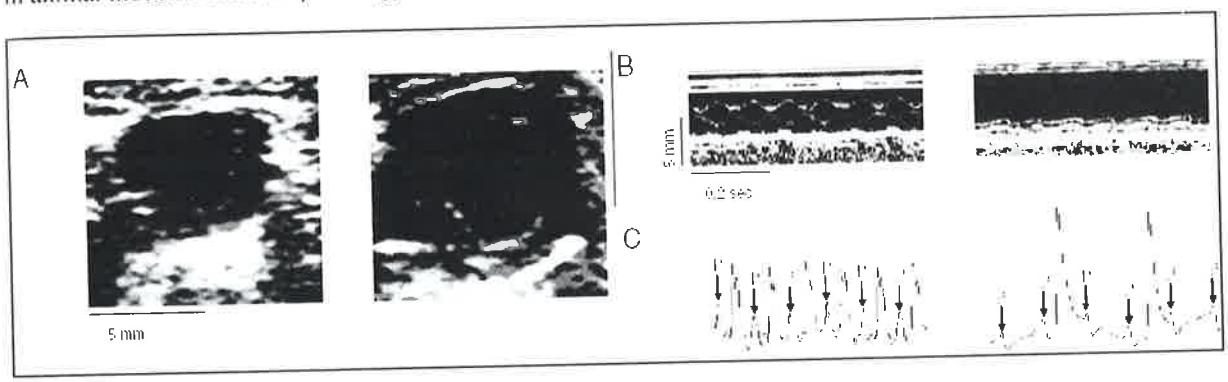
LV function expressed by fractional shortening or ejection fraction is better obtained by TM evaluation (Teichholtz formula) because of the 2D image rating. Even with 100 to 200 image/sec. calculation of Ejection Fraction by 2D methods is critical then heart rate reaches 300 b/min. or more. The duration of systole in awaked mice does nether exceed 100 ms with a mean of 7.5 bps. Systolic thickening of the septum or of the posterior wall can be nicely calculated from the same M-mode frames which also allows detection of ischemic areas. Pulsed tissue Doppler can be applied on both sides of the mitral annulus. Apical four chamber view is mostly difficult to obtain in mice but can be easily obtained in rabbits and rats.

Pulsed wave Doppler of the aortic flow is a very useful tool to evaluate systolic volume with the ITV calculation, filling of the left ventricle by the pulse wave Doppler is more difficult to study because of the heart rate, the brevity of diastole and also difficulties to obtain good tracings.

We have defined conditions in which contrast echo can be performed in mice or rats with Sonovue, a recently developed contrast agent. Used to obtain cavitary contrast Sonovue is effective when administered by bolus of 30 to 50 μl in rats, 20 μl in mice.

In contrast to humans, circulation of Sonovue (or destruction) is very fast due to the high frequency of imaging but not only to the high mechanical index, all the compound disappearing after 5 or 6 beats. Contrast allows a nice imaging of the pulmonary artery and of the left ventricle when administered by the jugular vein. Aorta is not or

very briefly visible, the contrast disappearing quickly at that level, even when increasing the administered dose. We had not the opportunity to make chronic infusions in our experimental set. With the S12 probe we could see that at the rate of 100 images/s, mechanical index carrying bubble destruction was about 0.8 to 1.2 but at 200 frames/s destruction of contrast was effective with a mechanical index of 0.3. Generally in mice and rats with contrast, the cavity imaging was less satisfactory with the S12 than with the 15L6 probe. Myocardial contrast enhancement was not evident after Sonovue injections even when dealing with low mechanical index and reduced rate of imaging. Impression was given of brightness of the endocardium increasing resolution of the interface of endocardium and cavity and allowing reduction of the gain of the ultrasonic beam. During that study densitometry was not available on our system, but we are confident that densitometry should increase the ability of Sonovue to enhance myocardial contrast.
Acoustic quantification (AQ) could be used with the S12 probe with good results but the calculated EF values were higher then those obtained with M-mode analysis when obtained without adequate gain settings. Actually Echocardiography and Doppler technology which are of great usefulness in human cardiology are now currently used in animal experimental laboratories. Standardization of procedures in mice at the European level is actually in progress through the "Eumorphia" program. So, applications derived from human cardiology have now been adapted to the study of the cardiac phenotype in transgenic animals or in models reproducing human pathology. Their performance is also important in pharmacology allowing the tests of new therapeutic hypothesis in animal models of human pathology.



A: 2D Sax in conscious 8 week old mice: left: normal mouse, right: Friedreich ataxia model.

B: M-mode tracings corresponding to A.

C: ECG: left: normal mouse, right: Friedreich ataxia model with complete atrio ventricular block.