Clinical Implications of Cardiovascular Variability

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- Heart rate variability (HRV) is beat to beat variation in heart rate (i.e. in R-R intervals) under resting conditions. These beat to beat variations occur due to continuous changes in the sympathetic and parasympathetic outflow to the heart.

- HRV has been shown to be a good tool to quantify the tone of autonomic nervous system to the myocardium.

- Methods used to detect beats include: ECG, blood pressure, and the pulse wave signal derived from a photoplethysmograph(PPG).

- ECG is considered superior because it provides a clear waveform, which makes it easier to exclude heartbeats not originating in the sinoatrial node.

- The main inputs are
  1. The sympathetic,
  2. The parasympathetic nervous system (PSNS) and
  3. Humoral factors.

- Though HRV can be measured over any length of recorded ECG, as per the guidelines of Task Force (1996) at least 5 minutes of ECG must be recorded to quantify Sympathetic and Parasympathetic tone.

- To standardize physiological and clinical studies, two types of recordings should be used whenever possible:

(a) short-term recordings of 5 minutes made under physiologically stable conditions processed by frequency domain methods and/or

(b) nominal 24-hour recordings processed by time-domain methods.

Physiological factors influencing HRV

- Age
- Gender
- Circadian rhythm
- Respiration
- Body position
- Food ingestion
- Medication

Drugs known to affect cardiac autonomic functions may be stopped after consultation with the physician for 2 days prior to testing.

- Anticholinergics (including antidepressants, antihistamines, and over-the-counter cough and cold medications),
- 9- α -flurocorticone,
- Diuretics,
- Sympathomimetic (α and β agonist) and
- Parasympathomimetic agents

- Although HRV has been the subject of numerous clinical studies investigating a wide spectrum of cardiological and noncardiological diseases and clinical conditions, a general consensus of the practical use of HRV in adult medicine has been reached only in two clinical scenarios.

- Depressed HRV can be used as

  => a predictor of risk after acute MI and

  => as an early warning sign of diabetic neuropathy

Myocardial infarction

- The majority of patients who survive acute MI do well except some who develop recurrent angina, re-infarction, ventricular arrythmias or sudden death.

- Thus a major goal of risk stratification is to identify population at risk for subsequent morbidity and mortality

- Risk of sudden death is highest in the first year after infarction. The major causes of sudden death are ventricular tachycardia and ventricular fibrillation.

- Currently, the 1-year risk of malignant arrhythmia developing in an MI survivor after hospital discharge is 5% or less.

- In patients with an acute MI the absence of respiratory sinus arrhythmias is associated with an increase in "in-hospital" mortality.

- The association of higher risk of postinfarction mortality with reduced HRV was first shown by Wolf et al in 1977.

- Depressed HRV after MI may reflect a decrease in vagal activity directed to the heart, which leads to prevalence of sympathetic mechanisms and to cardiac electrical instability.

- In the acute phase of MI, the reduction in 24-hour SDNN is significantly related to decreased left ventricular ejection fraction(LVEF), peak creatine kinase, and Killip class.

Decreased heart rate variability and its association with increased mortality after acute myocardial infarction.

Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ.

- To test the hypothesis that HRV is a predictor of long-term survival after acute MI, the Holter tapes of 808 patients who survived AMI were analyzed.
- HRV was defined as the SDNN in a 24-hour ECG recording made 11 +/- 3 days after AMI.
- Mean follow-up time was 31 months.
- Of all Holter variables measured, HRV had the strongest univariate correlation with mortality.
- Relative risk of mortality was 5.3 times higher in the group with HRV < 50 ms than the group with HRV >100 ms.
- HRV remained a significant predictor of mortality after adjusting for clinical, demographic and LVEF. A hypothesis to explain this finding is that decreased HRV correlates with increased sympathetic or decreased vagal tone, which may predispose to ventricular fibrillation

Am J Cardiol. 1987 Feb 1;59(4):256-62.

- Spectral analysis of HRV in patients surviving an acute MI revealed a reduction in total and in the individual power of spectral components.

- However, when the power of LF and HF was calculated in normalized units, an increased LF and a diminished HF were observed.

- The predictive value of HRV is independent of other factors established for post-MI risk stratification, such as :

  =>depressed LVEF,

  =>increased VPC, and

  =>presence of late potentials.

- Even in group with LVEF< 30%, low SDNN more than doubles the risk.

Risk stratification for arrhythmic events in postinfarction patients based on heart rate variability, ambulatory electrocardiographic variables and the signal-averaged electrocardiogram

Thomas G. Farrell et al.

- The value of HRV, ambulatory ECG and the signal-averaged ECG in the prediction of arrhythmic events (sudden death or life-threatening ventricular arrhythmias) was assessed before hospital discharge in 416 consecutive survivors of acute MI.
- During the follow-up period (range 1 to 1,112 days), there were 24 arrhythmic events and 47 deaths.
- HRV <20 ms, late potentials, VPC frequency, LVEF<40% and Killip class were identified as significant univariate predictors of arrhythmic events.
- Out of this, only impaired HRV<20msec, followed by late potentials remained independent predictors of arrhythmic events.
- On multivariate analysis the combination of impaired HRV and abnormal late potentials was the best independent combination for predicting arrhythmic events (a sensitivity of 58%, a positive predictive accuracy of 33% and a relative risk of 18.5 for arrhythmic events) and was superior to other combinations including those incorporating LVEF, ambulatory ECG, VPC frequency.

J Am Coll Cardiol. 1991;18(3):687-697.

- These results suggest that a simple method of assessment based on HRV and the signal-averaged ECG can select a small subgroup of survivors of MI at high risk of future life-threatening arrhythmias and sudden death.

ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction)

- An international study, involving 25 centres in Europe, U.S.A. and Japan enrolled 1284 patients with a recent MI.
- HRV as SDNN and baroreflex sensitivity (BRS) was calculated. 21 months of follow-up.
- SDNN<70 ms or BRS<3·0 mmHg were independent predictors of cardiac mortality with a RR of 3·2 and 2·8.
- Association of low SDNN or BRS with LVEF< 35% carried a relative risk of 6·7 and 8·7, respectively.
- 2-year mortality was 17% when both SDNN and BRS values were depressed and only 2% when both were well preserved.

Lancet 1998 feb14;351:478-84

- For prediction of all-cause mortality, the value of HRV is similar to that of LVEF.

- However, HRV is superior to LVEF in predicting arrhythmic events (sudden cardiac death and ventricular tachycardia).

- This permits speculation that HRV is a stronger predictor of arrhythmic mortality rather than nonarrhythmic mortality.

Predictive value of depressed HRV in MI

- The predictive value of depressed HRV increases with increased length of recording.
- The assessment of HRV from short-term recordings can be used for initial screening of survivors of acute MI. Such an assessment has similar sensitivity but lower specificity for predicting patients at high risk compared with 24-hour HRV.
- Only patients with depressed 5 min SDNN may undergo 24-hour holter monitoring to be a cost effective method.
- Positive predictive accuracy is upto 31% in short term HRV versus upto 41% in 24 hour recording.

Mechanism of depressed HRV in MI

- The changes in the geometry of a beating heart due to necrotic and noncontracting segments may abnormally increase the firing of sympathetic afferent fibers by mechanical distortion of the sensory endings.

- Reduced responsiveness of sinus nodal cells to neural modulations following MI.

Pathophysiological Considerations

- Data suggest that depressed HRV is not a simple reflection of sympathetic overdrive and/or vagal withdrawal,

  But it also reflects depressed vagal activity, which has a strong association with the pathogenesis of ventricular arrhythmias and SCD.

Development of HRV After Acute MI

- The time after acute MI at which the depressed HRV reaches the highest predictive value has not been investigated comprehensively.

- Nevertheless, the general consensus is that HRV should be assessed shortly before hospital discharge, that is, approximately 1 week after index infarction.

- HRV is decreased early after acute MI and begins to recover within a few weeks; it is maximally but not fully recovered by 6 to 12 months after MI.

The gradual improvement in autonomic indices has been attributed to

- reversal of ischemia,
- washing out of ischemic metabolites,
- receptor necrosis and
- adaptation of receptors to continuing mechanical and chemical stimuli.

Time course of recovery of heart period variability after myocardial infarction

J.Thomas Bigger Jr

- To determine the time course and magnitude of recovery for the measures of HRV spectrum(ULF, VLF,LF and HF power plus total power) , 68 patients in the Cardiac Arrhythmia Pilot Study (CAPS) placebo group having 24-h ECG recordings at baseline, 3, 6 and 12 months after MI were studied.

- HRV measures compared to those found in 95 normal persons of similar age and gender.

  =>At baseline it was one third to one half.

  =>Substantial increase occurred between baseline and 3-month recording ($p < 0.001$).

  =>Between 3 and 12 months, the values were quite stable

  =>However, even at 12 months HRV measures were one half to two thirds the values found in the sample of 95 normal persons.

Summary and recommendations for interpreting predictive value of depressed HRV after acute myocardial infarction

- The following facts should be noted when exploiting HRV assessment in clinical studies and/or trials involving survivors of acute myocardial infarction.

1. Depressed HRV is a predictor of mortality and arrhythmic complications independent of other recognised risk factors.

2. There is a general consensus that HRV should be measured approximately 1 week after index infarction.

3. Although HRV assessed from short-term recordings provides prognostic information, HRV measured in nominal 24-h recordings is a stronger risk predictor. HRV assessed from short-term recordings may be used for initial screening of all survivors of an acute MI.

4. No currently recognised HRV measure provides better prognostic information than the time–domain HRV measures assessing overall HRV (e.g. SDNN or HRV triangular index).

5. A high risk group may be selected by the dichotomy limits of SDNN <50 ms or HRV triangular index <15.

6. The predictive value of HRV alone is modest, although it is higher than that of any other so far recognised risk factor.

7. To improve the predictive value, HRV may be combined with other factors. However, optimum set of risk factors and corresponding dichotomy limits have not yet been established.

Diabetic neuropathy

- Autonomic neuropathy in DM is characterized by early and widespread neuronal degeneration of small nerve fibers of both sympathetic and parasympathetic tracts.

- Once clinical manifestations of diabetic autonomic neuropathy (DAN) supervene, the estimated 5-year mortality is approximately 50%.

- The following abnormalities in frequency HRV analysis are associated with DAN:

  (1) reduced power in all spectral bands -the most common finding

  (2) failure to increase LF on standing, which is a reflection of impaired sympathetic response or depressed baroreceptor sensitivity,

  (3) abnormally reduced total power with unchanged LF/HF ratio.

- A reduction in time domain parameters of HRV seems not only to carry negative prognostic value but also to precede the clinical expression of autonomic neuropathy.

Cardiac transplantation

- In resting supine position after cardiac transplantation the beating of heart is essentially metronomic, giving a fixed stable heart rate. Resting heart rate is higher than in normal subjects.

- A very reduced HRV with no definite spectral components is reported in patients with a recent heart transplant.

- The appearance of discrete spectral components in a few patients is considered to reflect cardiac reinnervation.

- This reinnervation may occur as early as 1 to 2 years after transplantation and is usually of sympathetic origin.

- There is no evidence that heart transplant subjects up to 52 months after transplantation have any vagally mediated HRV.

- Thus HF respiratory related variations of heart rate in transplant subjects appear to be mediated solely by nonautonomic mechanisms such as respiratory related atrial stretch.

Myocardial dysfunction

- Prognosis of heart failure patients are weakly related to the extent of LV dysfunction , while neurohormonal mechanisms,particularly the ANS, appear to possess a relevant independent weight.

- In this condition characterized by signs of sympathetic activation, a relation between changes in HRV and the extent of LV dysfunction was reported.

- Both vagal and sympathetic control of heart rate are deranged in heart failure.

- In fact, whereas the reduction in time domain measures of HRV seemed to parallel the severity of the disease, the relationship between spectral components and indices of ventricular dysfunction appears to be more complex.

- Inspite of the signs and measures of increased overall sympathetic drive in heart failure, the presence of depressed HRV suggests impaired sympathetic neural discharge to sinus node.

- Sympathetic neural endings to heart are decreased suggesting neural sympathetic damage at the cardiac level in heart failure.

HRV and sudden death

- SCD survivor at high risk of a second episode can be distinguished on the basis of their response to programmed ventricular stimulation, ie whether or not they developed sustained runs of rapid monomorphic tachycardia. However the inducibility criterion may be of uncertain utility in recent MI and cardiomyopathy.

- HRV is markedly depressed in SCD survivors compared with normal controls

- In a study, the combination of low HRV(SDNN<30 msec) and inducibility correctly identified all SCD survivors who subsequently died during a 100 month follow up.

- However, the specificity and predictive accuracy of altered HRV in predicting imminent or future fatal arrhythmia events have still been relatively low.

- Therefore, the widespread clinical application of this method has not been established for monitoring the HR behaviour in individual patients.

- Current indications for ICD implantation for primary prevention of SCD are based mainly on a hemodynamic parameter, LVEF <30–40% both in post-MI and in non-ischaemic cardiomyopathies.

- Among electrophysiological parameters, only non-sustained ventricular tachycardia during Holter monitoring and induction of VT on electrophysiological testing, is recognized in current guidelines as predictors of benefit from ICD implant for primary prevention of SCD.

- Consistent evidence have shown that low HRV in combination with reduced LVEF contribute to identification of patients at high risk of SCD.

- However, according to current guidelines for the prevention of SCD, HRV was useful for risk stratification (Class IIb recommendation), but evidence was not robust enough to include HRV as a predictor in risk stratification for primary ICD implantation

Modifications of HRV
by
specific interventions

- The target is the improvement of cardiac electrical stability, and HRV is just a marker of autonomic activity.

- Despite the growing consensus that increases in vagal activity can be beneficial, it is not as yet known how much vagal activity (or its markers) has to increase in order to provide adequate protection.

ß-Adrenergic blockade and HRV

- The data on the effect of beta-blockers on HRV in post- MI patients are surprisingly scanty.
- It is of note that ß-blockade prevents the rise in the LF component observed in the morning hours.
- Despite the observation of statistically significant increases, the actual changes are very modest.

Thrombolysis and HRV

- HRV was higher 90 minutes after thrombolysis in the patients with patency of the infarct-related artery.

- However, this difference was no longer evident when the entire 24 hours were analyzed.

Exercise training and HRV

- After training, HRV (SDNN) increased by 74%, and all animals survived a new ischemic test.

Fetal HRV

- Fetal and neonatal HRV is an important area of investigation, and it might provide early information about fetal and neonatal distress and identify those at risk for sudden infant death syndrome.

- Most of the preliminary work in this field was carried out in the early 1980s before the more sophisticated power spectral techniques became available.

- Insight into autonomic maturation in the developing fetus also might be possible through the proper application of these techniques.

ACC/AHA Guidelines and Recommendations for Measurement of HRV to Assess Risk for Future Cardiac Events in Patients Without Symptoms From Arrhythmia

(Developed in Collaboration With the North American Society for Pacing and Electrophysiology)

Class I

- **None**

Class IIa

- ***None***

Class IIb

- **Post-MI patients with LV dysfunction**
- **Patients with CHF**
- **Patients with idiopathic hypertrophic cardiomyopathy**

Class III

- **Post-MI patients with normal LV function**
- **Diabetic subjects to evaluate for diabetic neuropathy**
- **Patients with rhythm disturbances that preclude HRV analysis (ie, atrial fibrillation)**

Ongoing project in our department

Title: Is Heart rate variability related to the presence of viable myocardium in patients after first anterior myocardial infarction

Aim: To assess the differences in average values of heart rate variability parameters among conservatively managed post myocardial infarction patient with or without viable myocardium.

Method:

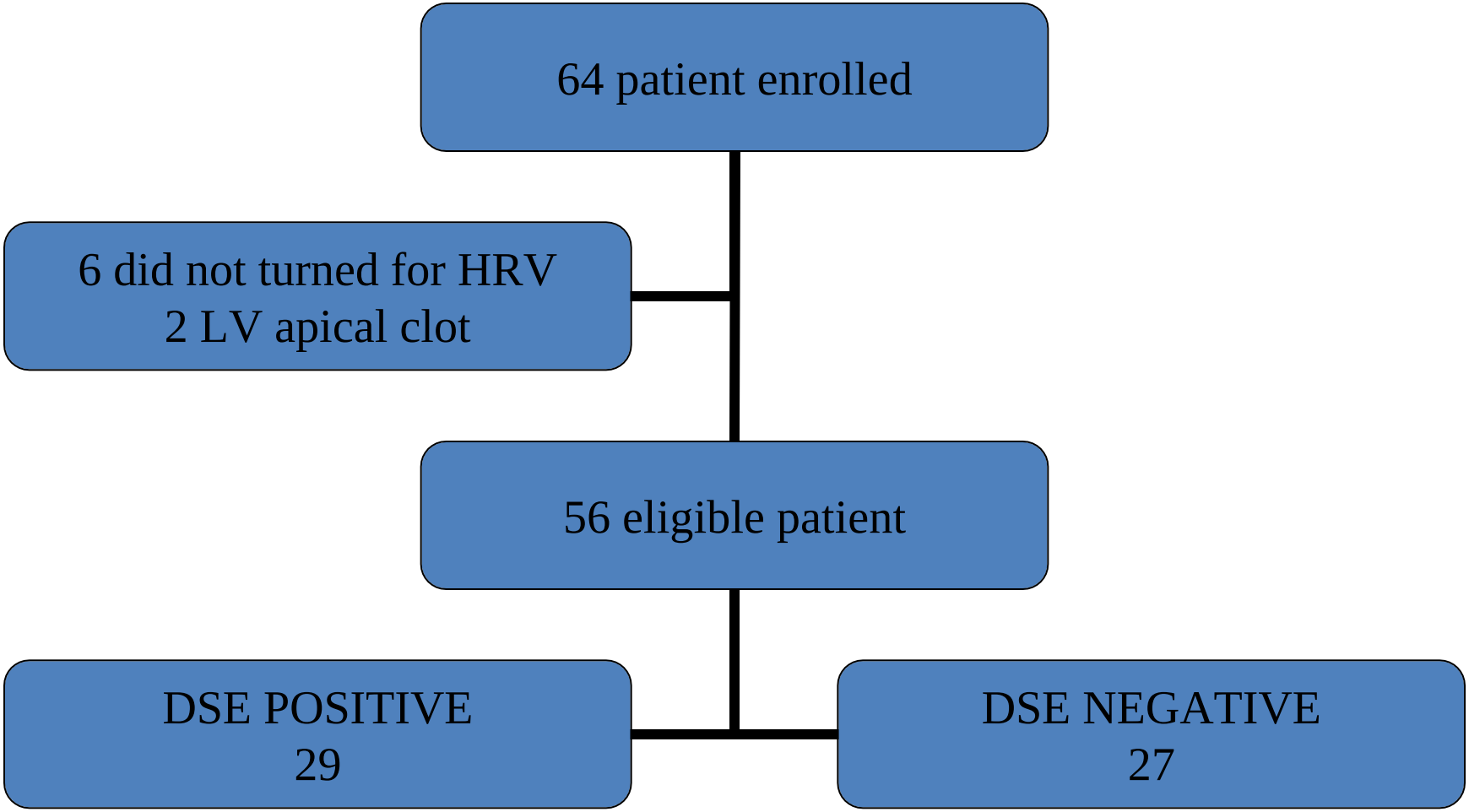
Patients diagnosed with a first anterior wall STEMI treated conservatively and successfully with thrombolytics**.**

↓

They underwent Dobutamine stress echocardiography at least 2 weeks post myocardial infarction.

↓

Time domain and frequency domain parameters of HRV were studied and compared in both groups


64 patient enrolled
6 did not turned for HRV
2 LV apical clot
56 eligible patient
DSE POSITIVE
29
DSE NEGATIVE
27

TAKE HOME MESSAGE

- Heart rate variability has considerable potential to assess the role of autonomic nervous system fluctuations in normal healthy individuals and in patients with various cardiovascular and non-cardiovascular disorders.

- HRV studies should enhance our understanding of physiological phenomena, the actions of medications, and disease mechanisms.

- Large prospective longitudinal studies are needed to determine the sensitivity, specificity, and predictive value of HRV in the identification of individuals at risk for subsequent morbid and mortal events.

- Determining the prognostic value of HRV for identification of high-risk patients has been the objective of many experimental and clinical studies in the last few decades. Nevertheless, the position of HRV in modern cardiology is still uncertain.

- Currently, according to the ACC/AHA Guidelines for Ambulatory Electrocardiography, only patients with left ventricle dysfunction after myocardial infarction, without symptoms of arrhythmia, may benefit from HRV measurements for risk assessment

THANK YOU..