Cardiac autonomic neuropathy

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April 12, 2005

Anatomy

- Vagal and sympathetic nerve fibers intermingle in all regions of the heart
- Central mechanisms (hypothalamus) can be up- or down-regulated by long term stimuli
  - Exercise training
  - Heart failure
  - Hypertension
  - Diabetes

Testing cardiac autonomic function

- Clinical reflex tests
  - Heart rate variation
    - Deep breathing
    - Lying to standing posture
    - Valsalva
  - BP response to standing
- Other methods
  - Plasma norepinephrine
  - Heart rate variability
    - Primary technique of evaluation due to low cost, good reproducibility, and ease
  - PET
  - MIBD (I^{123}) scintigraphy

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Heart rate variability
Time Domain

- Summarizes short or long term variability in RR (NN) intervals
  - Excludes ectopic (nonsinus beats)
- Statistical Measures
  - SDNN – std deviation of all RR intervals over 24 hours
  - SDANN – std deviation of average RR interval of each 5 minute period in a 24 hour period
  - ASDNN – average of all std deviations for each 5 minute period in 24 hours
  - pNN50 – proportion of NN intervals varying >=50 ms
- Typically measured over 5 minutes – 1 hour

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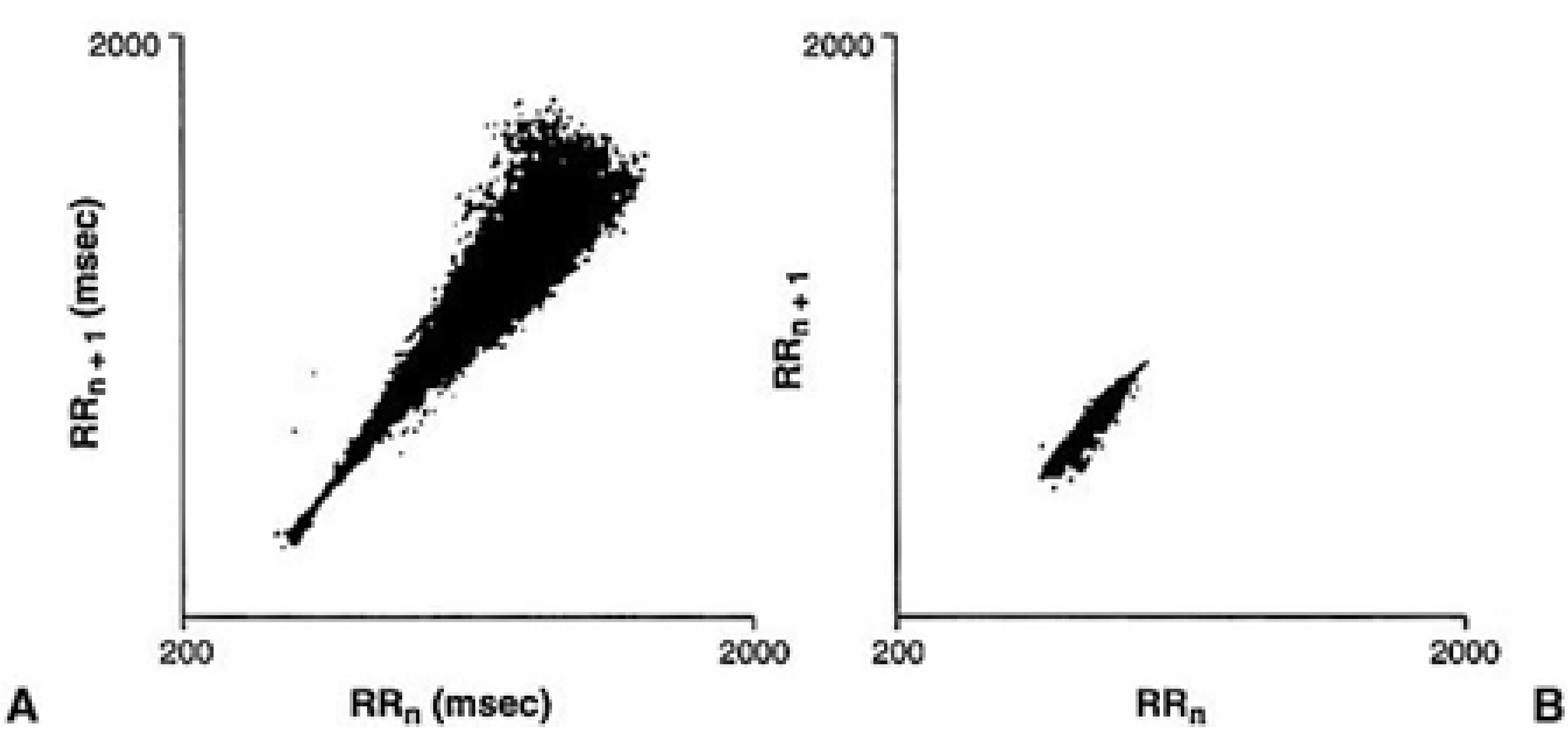
Variable	Units	Definition
Time domain–statistical measures		
Night–day difference	Millisecond	Difference between the average of all the normal RR intervals at night (24:00 to 05:00) and the average of all the normal RR intervals during the day (07:30 to 21:30)
SDNN	Millisecond	Standard deviation of all normal RR intervals in the entire 24-h ECG recording
SDANN	Millisecond	Standard deviation of the average normal RR intervals for all 288 5-min segments of a 24-h ECG recording (each average is weighted by the fraction of the 5 min that has normal RR intervals)
ASDNN	Millisecond	Average of the standard deviations of normal RR intervals for all 288 5-min segments of a 24-h ECG recording
r-MSSD	Millisecond	Root mean square successive difference, the square root of the mean of the squared differences between adjacent normal RR intervals over the entire 24-h ECG recording
pNN50	Percent	Percent of differences between adjacent normal RR intervals that are greater than 50 ms computed over the entire 24-h ECG recording
NN50	None	Number of adjacent normal RR intervals that are greater than 50 ms counted over the entire 24-h ECG recording
Time domain–geometric measures		
Heart-rate variability triangular index	None	Total number of NN intervals divided by the number of NN intervals in the modal bin of a histogram of all NN intervals with a bin width of 7.8125 ms (for a sampling rate of 128/sec)
TINN	Millisecond	Baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals
Frequency domain measures		
Total power	Square milliseconds	The energy in the heart period power spectrum up to 0.40 Hz
Ultra low-frequency power	Square milliseconds	The energy in the heart period power spectrum up to 0.0033 Hz
Very low-frequency power	Square milliseconds	The energy in the heart period power spectrum between 0.0033 and 0.04 Hz
Low-frequency power	Square milliseconds	The energy in the heart period power spectrum between 0.04 and 0.15 Hz
High-frequency power	Square milliseconds	The energy in the heart period power spectrum between 0.15 and 0.40 Hz
Low-frequency to high-frequency ratio	None	The ratio of low- to high-frequency power
α	None	Slope of log(power) on log(frequency) between 0.01 and 0.0001 Hz on a log-log plot

ASDNN, average standard deviation of normal to normal intervals in 5-minute intervals calculated over 24 hours; ECG, electrocardiography; NN, normal to normal intervals; NN50, number of times that successive RR intervals differed by greater than 50 ms in a 24-hour period; pNN50, proportion of differences between successive normal to normal intervals that are greater than 50 ms; r-MSSD, square root of the mean squared successive differences of normal to normal intervals; SDANN, standard deviation of the average normal to normal intervals for the 288 5-minute intervals in a 24-hour continuous electrocardiographic recording; SDNN, standard deviation of normal to normal intervals over a 24-hour period.
[a]The physiologic interpretation of these measures of RR variability is given in the text.
From Jiang W, Hayano J, Coleman ER, et al. Relation of cardiovascular responses to mental stress and cardiac vagal activity in coronary artery disease. *Am J Cardiol* 1993;72:551–554, with permission.



Lorenz or Poincaré plots. The current RR interval (RR_n) is plotted on the x-axis, and the subsequent RR interval (RR_{n+1}) is plotted on the y-axis. Panel A is a plot from a healthy 52-year-old man that shows a wide range of RR intervals and shows greater dispersion of RR interval at longer RR intervals. Panel B is a plot from a 61-year-old man with heart failure that shows a decreased range of RR intervals and does not show greater dispersion of RR interval at longer RR intervals

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Heart Rate Variability Frequency Domain

- Can be measured in a 5 minute Power Spectrum
- Fast Fourier Transform density of RR intervals
- Shows overall variability, and frequency specific modulations
  - High frequency (0.18-0.40 Hz), varies with respiration – marker of Vagal activity
  - Low frequency (0.03-0.15Hz), more correlative with sympathetic activity

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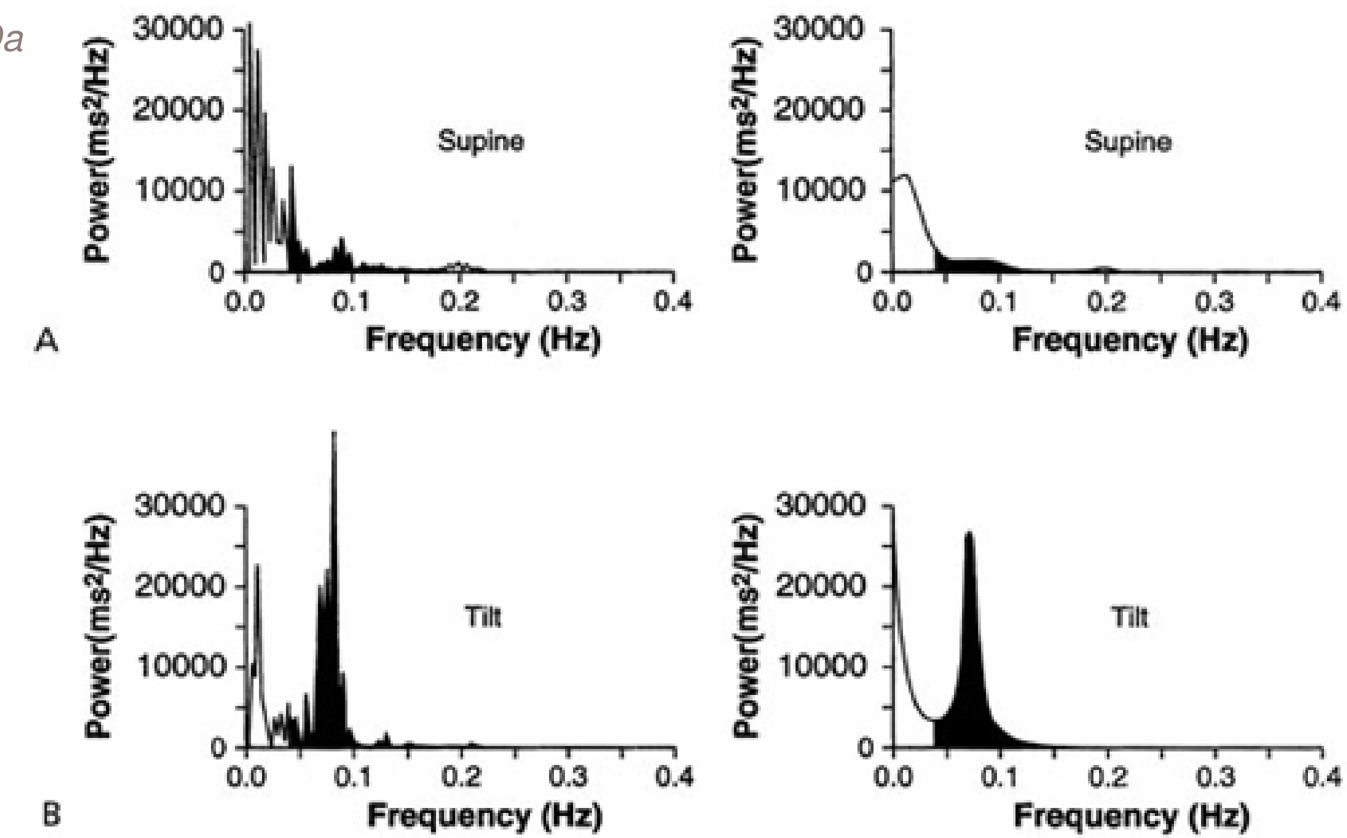

Power spectral analysis of RR-interval time series. The left panels show fast Fourier transform (FFT) analysis of two 5-minute recordings of RR intervals. The left panel of A shows the FFT of a recording made supine and resting; the left panel of B shows the FFT of a recording made during 60-degree head-up tilt. The right panels show the results of autoregression analysis of the same two 5-minute recordings. The autoregressive algorithm smooths the data, but gives almost identical areas under the curves as the FFT algorithm in the frequency bands of interest. In the supine recording, there is a peak at approximately 0.20 Hz in the high-frequency (HF) power band, and a peak at approximately 0.08 Hz in the low-frequency (LF) power band. More than one-half the power is in the very low-frequency power band. Both methods show a decrease in HF power and a marked increase in LF power during head-up tilt.

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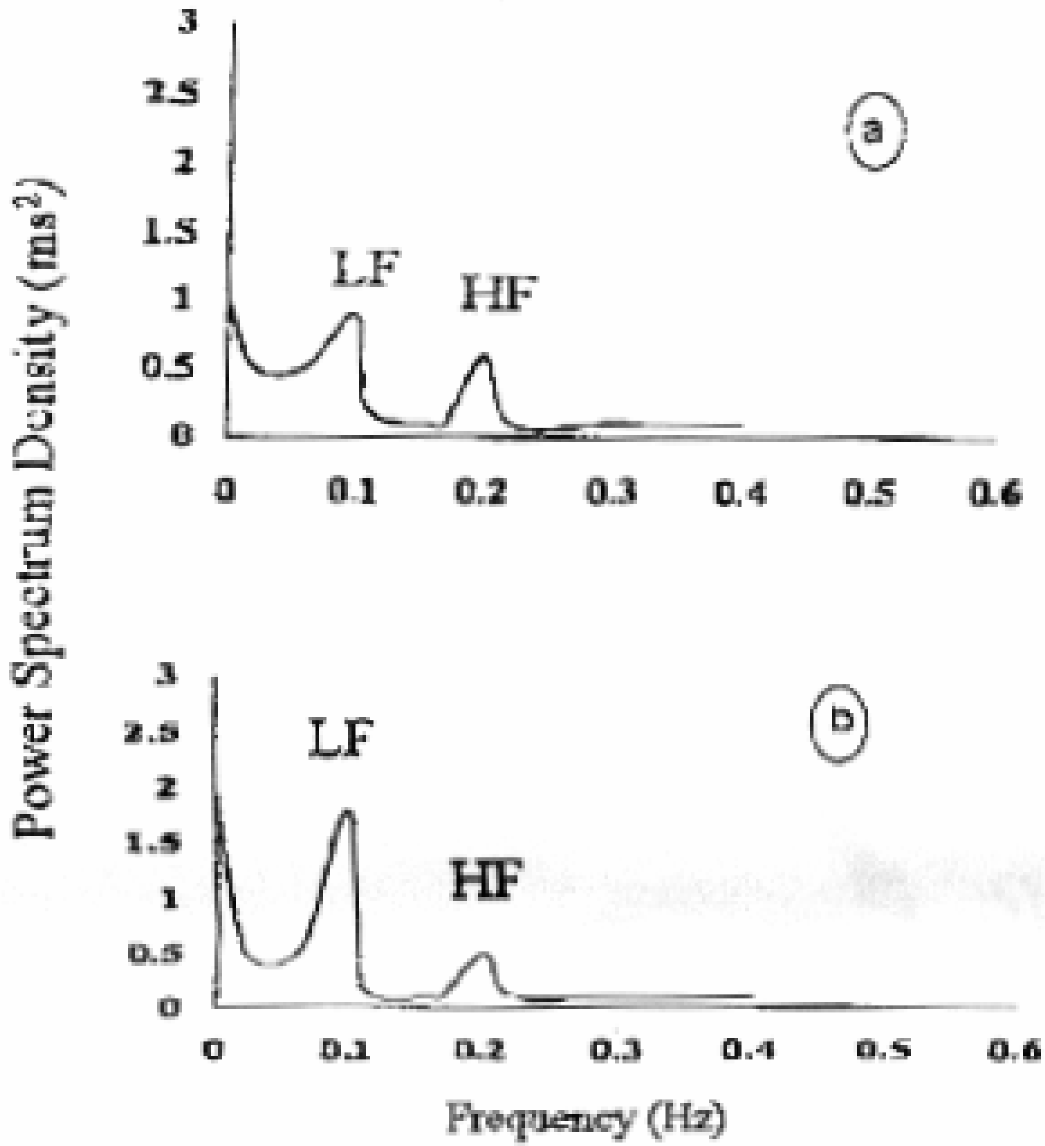

Figure 2 An example of the spectral analysis of RR interval variability in a healthy subject (a) and a patient with Type II diabetes (b)

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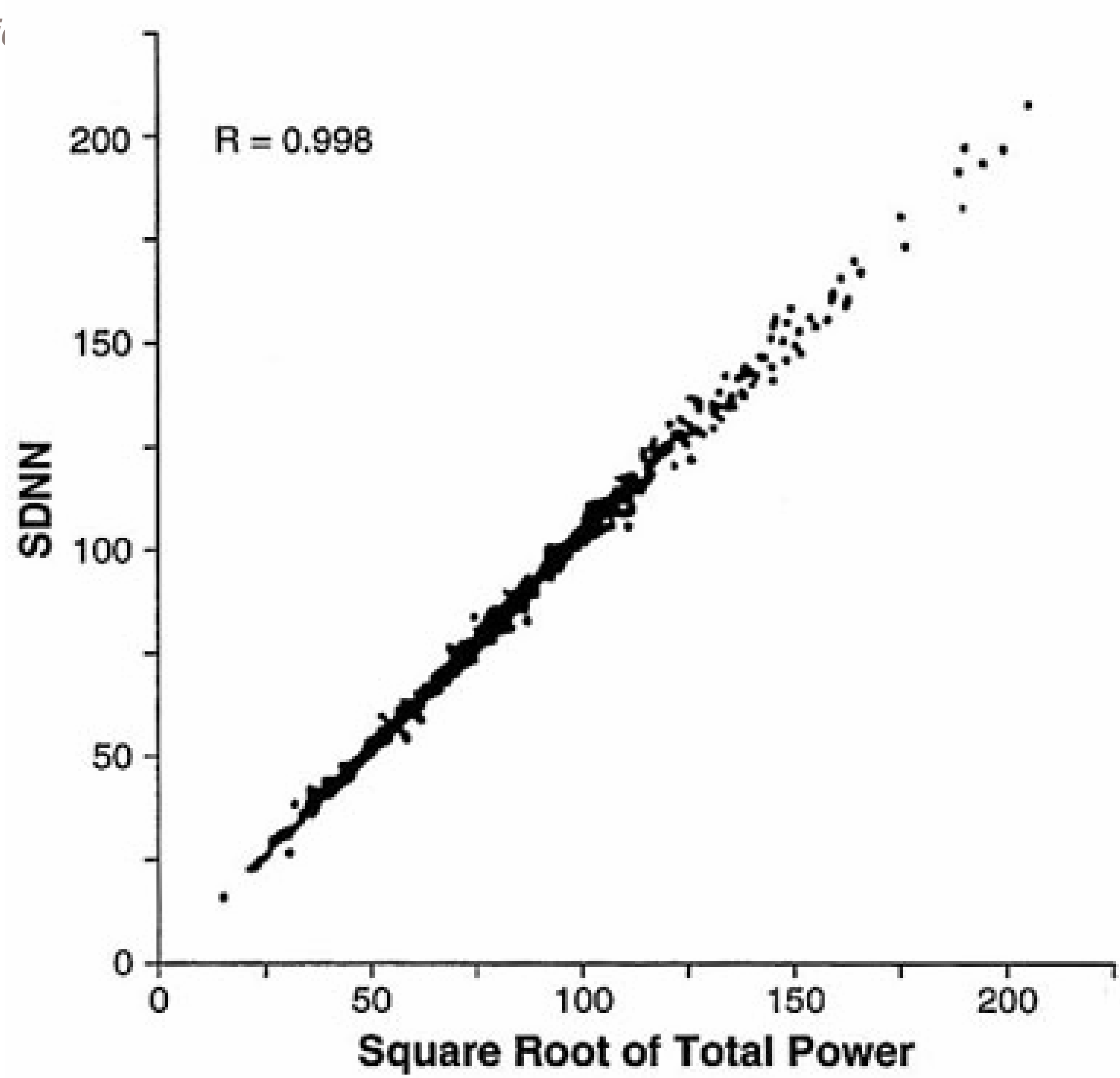

Time domain and Frequency domain methods have good correlation

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HRV

- LF/HF ratio correlates with autonomic vagal/sympathetic activity
- Unbalanced tone (especially sympathetic dominent) associated with increased cardiovascular mortality in DM type II
- Likely cause of sudden cardiac death in diabetics despite absence of structural heart disease

Diabetes and Cardiovascular Autonomic Neuropathy (CAN)

- Damage to autonomic nerve fibers innervating heart and blood vessels
- Causes abnormalities in heart rate control and hemodynamics
- Reduced HR variability is the earliest sign of CAN
- Two studies have shown increased mortality of diabetics with CAN (53%/27% at 5 years) vs. diabetics without CAN (15%/8% at 5 years)
- However, uncertain exact mechanism by which CAN increases mortality

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Cause of autonomic dysfunction

- Hyperinsulinemia/Insulin resistence
  - Insulin increases sympathetic activity
    - Prolonged = sustained stimulation of cardiac sympathetics
    - CNS effects at hypothalamus
    - Peripheral effects involve nitric oxide synthesis (mediator of endothelial function) and NEFA (non-esterified fatty acids)
      - Insulin stimulates NO production
      - NEFA's reduced by insulin therapy

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Therapy of CAN

- Improve nutrition
- Reduce alcohol and tobacco
- Glucose control
- Vitamin E – improves sympathetic balance in type 2 diabetics
- Metformin – decreases NEFAs and insulin resistance; improves autonomic balance

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References

- Manzella D and Paolisso G (2005). Cardiac autonomic activity and Type II diabetes mellitus. Clinical Science 108, 93-99.
- Topol EJ et. al. Textbook of Cardiovascular Medicine, 2nd ed. Lippincott Williams & Wilkins, 2002.