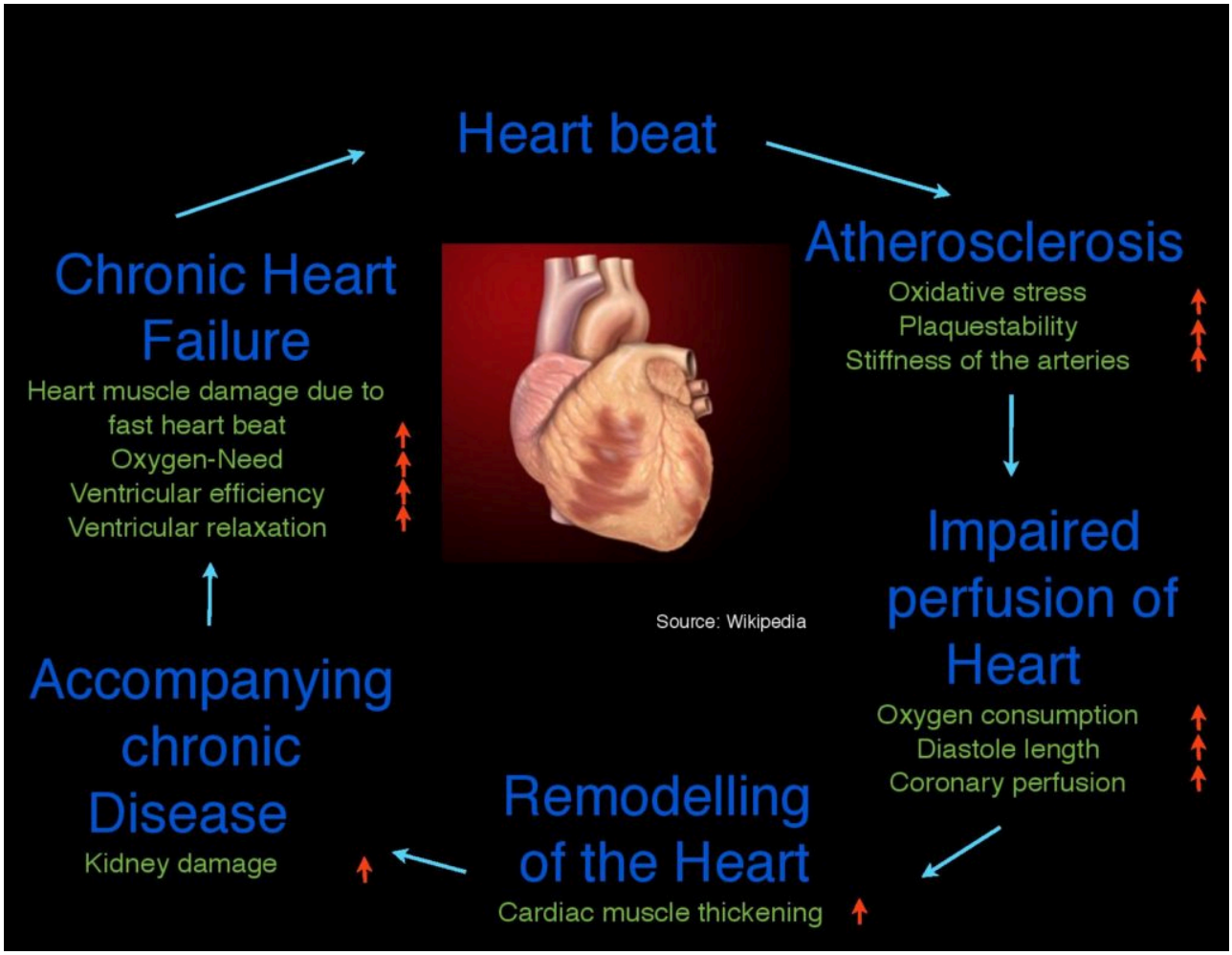
Evaluation of heart rate measurements in clinical studies - Which way to do it right?

100.000 times a day - this is the daily number of heart beats in human beings. This huge workload normally will pass by unobserved in a healthy being, but in a patient with heart disease any alteration of the heart beat is accompanied by discomfort.

There are several medications used in the treatment of heart disease that will slow down the heart beat. Usually, beta-blockers, Calcium-channel-blockers and extract from a flower - digitalis - are used for this purpose.

Sometimes the above medications are limited in their use by collateral damage to the body, i.e. depression and impotence as a consequence of the use of beta-blockers or hypotension due to the use beta-blockers as well as Calcium-channel-blockers. Therefore, pharmacological research looks for alternative medications (e.g. ivabradin, cilobradin) acting specifically on the sinus node. The sinus node is responsible for the generation of the normal heart rhythm and may compared to a spark plug in a car engine. The amount of “sparks” generated alter the power generated by the “engine” heart. If the number of “sparks” are reduced by the above medication the power generated by the “engine” heart will also be reduced, and as a consequence end up reducing oxygen consumption of the heart and prolong a phase of the heart cycle - the diastole - essential to the proper functioning of the heart. Furthermore, the stress put on heart wall and vessels will be diminished. This is all supposed to result in a longer life expectancy in patients with heart disease.



Clinical studies as well as clinical trials are conducted to demonstrate the efficacy of heart lowering therapy on symptoms and prognosis of patients with heart failure and coronary heart disease. In these studies, dosage of heart rate lowering agents is mostly based on measurements of heart rate in ECG tracings at rest.

There are several uncertainties about the significance of a single heart rate measurement at rest. First, there is a variability of heart rate measurements within the day and from day to day. Secondly, no one knows whether there is a correlation of ECG derived values with “real world” measurements of heart rate by the patient during his daily activities. The lack of information on all these issues sheds some doubt on the significance of the results suggested by the studies by clinicians and the pharmaceutical industry.

To understand how well a single heart rate measurement at rest reflects the heart rate pattern during the whole day we investigated 102 patients with heart disease on heart rate lowering therapy. The patients recorded six measurements at rest during the day for a total of 6 days and three measurements per day under exercise conditions. In total 3559 heart rate measurements at rest and 1831 measurements under exercise conditions were recorded. Furthermore, we

performed a 24 h ECG recording and a bicycle ECG stress test.

For the first time we could show that measurements in ECG tracings at rest and based on self-assessment are comparable and reproducible. But under exercise conditions, heart rate measurements taken by bicycle ECG stress test and by 24-h ECG monitoring do not agree in a sufficient manor with measurements based on self-assessment.

In conclusion, in future clinical studies on the effect of heart lowering drugs, heart rate should be measured 1) at rest by self-reported heart rate measurements or by ECG tracings at rest, and 2) for an adequate assessment of heart rate under exercise conditions multiple stress ECGs and 24 h ECG recordings have to be performed.

Otherwise, doubt on the significance of the study results presented by clinicians and the pharmaceutical industry will remain.

Therefore, in future clinical studies on the effect of heart lowering drugs, (1) the self-reported heart rate measurements by the patient as well as the measurements taken by ECG tracings at rest seems to be reliable only at rest and (2) it seems reasonable to propose a standardized operating procedure comprising three treadmill ECG, and three 24-h Holter recordings for the evaluation of heart rate under exercise conditions.

Therefore, in future clinical studies on the effect of heart lowering drugs, (1) heart rate measurements may be taken by self-reported heart rate measurements by the patient as well as the measurements taken by ECG tracings at rest seems to be reliable only at rest and (2) it seems reasonable to propose a standardized operating procedure comprising three treadmill ECG, and three 24-h Holter recordings for the evaluation of heart rate under exercise conditions.

In addition, the natural variation in heart rate between day and night is not changed by the heart rate lowering medication and measurement of heart rate will not be affected by this natural variation.

Indeed, several scientific publications showed that an accelerated heart beat is responsible for 1) an earlier calcification of the heart and body vessels, 2) a pathological increase in the heart wall thickness, and 3) an increase in the number of heart attacks as well as disturbances of the heart rhythm. Furthermore, the reduction of the heart beat will result in a longer life expectancy in patients with heart disease.

Furthermore, a correlation of ECG derived values with “real world” measurements of heart rate by the patient during his daily activities has never been looked at.

There is also some uncertainty on the variability of heart rate measurements within the day and from day to day. Finally, the question arises how well a single heart rate measurement at rest

reflects the heart rate pattern during the whole day. The lack of information on all these issues sheds some doubt on the significance of the results suggested by the respective studies.

Marco Albanese
Herzzentrum Duisburg, Duisburg, Germany
Regionalspital Surselva, Ilanz, Switzerland

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