Heart’s memory in the transplanted heart

Giuseppe Guarini, Maria Ambrosini*, Camillo Cammarota**

*Aging Science Department, *II Institute of Cardiology, **Mathematics Department, La Sapienza University, Rome, Italy*

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Address:

Prof. Giuseppe Guarini

Piazza A. Baldini, 13
00141 Roma

With regard to its kinetic activity, the cardiac muscle can be compared to an electrofunctional apparatus with an automatic activity with cyclic trend. Blood, which distributes oxygen and all the elements needed to meet the metabolic and functional requirements of this apparatus, acts as its energy source.

While carrying on its dynamic activity, the heart is not necessarily dependent on the autonomic nervous system. In fact, as soon as it is implanted in recipient subjects, the transplanted heart, a complete denervated organ, is autonomously able to deal with any of its hemodynamic requirements. This functional autonomy is based on a complex system of processing and exchange of information that can be correctly analyzed only if connected to a memory effect . As we have already said in our previous studies, this cardiac memory must be interpreted as all the information remaining between an operating cycle and the subsequent one in the kinetic activity of the heart .

The presumptive memory of the cardiac dynamic system, also fascinatingly called heart s memory , is currently being studied by cardiologists, cardiophysiologists and bioengineers. The research on this topic is however still scanty and sketchy due to the difficulty in turning theoretical research models into valid and reliable experimental patterns.

The concept of heart s memory was first elaborated in 1871 by Henry Pickering Bowditch[1], when he defined the staircase phenomenon . Bowditch observed that, after each contraction, something was still able to influence the subsequent heart contraction. More than a century later, the concept of heart s memory was clearly defined by Mauricio Rosenbaum et al.[2]. In 1982 these authors observed a cardiac memory based on the constant morphologic modifications in the T wave of the ECG in patients suffering from spontaneous intermittent left bundle branch block, or in patients with block induced by atrial or ventricular pacing in which neither myocyte hypertrophy nor symptoms of ischemia or of a worsened hemodynamic heart function could be proved.

Rosenbaum et al. specifically reported that the modifications in the sequence of ventricular activation observed in the block can lead to two different modifications in ventricular repolarization. Remarking on the results of this research, Rosenbaum et al. regarded the electronic modifications in the T wave as the result of an information retention and storage phenomenon going on for days or weeks, even when the stimulus that led to the T wave modifications completely stopped. According to these authors, there are undoubted clinical effects in the sense that each modification in the phenomenological process of the ventricular activation may lead to pseudoprimary T wave modifications often going on, moreover, for a long time after the activity of the factor provoking these modifications has stopped. The electronic modulation of ventricular repolarization is in fact an electrophysiological mechanism which can explain different normal and anomalous configurations in the T wave and therefore prove the existence of the heart s memory .

Rosenbaum s research was followed by both clinical and experimental studies.

Clinical studies made it possible to observe the phenomenon described by Rosenbaum et al. also in patients suffering from other disorders: ventricular pacing, ventricular tachycardia, ventricular extrasystoles, and ventricular preexcitation.

Experimental studies, carried out by means of different methods on rabbits and dogs, made it possible to prove that myocardial cells are capable of remembering the previous modifications in repolarization even when the factors provoking these modifications have stopped their activity.

On the basis of these observations, now the problem of heart s memory is also influencing the research on the time sequence of the heartbeat, as shown by the original research on heart s memory carried out in 1995 by Goyal et al.[3]. They advanced a computerized two-dimensional research model of the kinetic activity of the myocardium. The model assumes a myocyte monolayer in which each cell is linked to the four nearby cells by means of a resistor and of a parallel capacitor. In this model, running for a very short span, artificially induced repolarization modifications can be recorded for no more than 5 consecutive beats.

The data collected in the literature show however that even nowadays it is very unlikely to formalize a molecular model that can describe the various complex mechanisms underlying the phenomenon called heart s memory at a structural and functional level. This is why, with the aim of highlighting the existence of heart s memory, regarded as the remaining information between a cardiac cycle and the subsequent one, we paid more attention to the tacogram indicating the cardiac impulse acceleration and/or deceleration in the time series of the heartbeat. To this end, we wish to stress our opinion, already formulated elsewhere, that, even if temporally connected both to the previous and to the subsequent one, each cardiac impulse is a specific and unique phenomenon in the history of each heart.

For our research on heart s memory we decided to use the mathematical analysis of the tacogram. Therefore, in each 24-hour Holter ECG we studied the autocorrelation and the spectrum analysis of the tacogram, both in a group of healthy individuals and in patients who received orthotopic heart transplantation more than 5 years previously.

The data we collected were analyzed by using sophisticated computer systems, which made possible for us to analyze a vast amount of information in a reasonable time span.

The tacogram results from the analysis of the time intervals between two consecutive R peaks in the ECG (also RR sequence). This sequence denoted Xl, X2, etc., is related to the instantaneous heart rate (b/min) by the relationship 60/xi if the time units of the xi s are seconds. The tacogram of the 24-hour Holter recording of the ECG appears to be nonstationary. Most of the mathematical techniques used in the analysis of time series work in a stationary situation. Hence we consider short windows in tacogram (typically 1000 values) or we consider the different series X2-Xl, X3-X2, etc., which show a satisfactory stationary situation.

The spectrum analysis of a time series is used to investigate the presence of periodicity in the data, by means of decomposition in harmonic components characterized by their frequency *f* (and period *l/f*). It provides a function, the frequency spectrum, which gives the weight *W (f)* corresponding to frequency *f* in the decomposition.

The autocorrelation function gives for each distance *d* the correlation index of the pair of variables that in the series occupy time positions that differ by *d*. If this function vanishes in the case of *d* greater than a given value, this value can be assumed to be the memory of the series.

The research was carried out on:
- a group of 15 healthy subjects made up of volunteers (mostly university students, male and female) with a good functional state of cardiac activity and with an efficient circulatory system;
- a group of 15 patients who underwent orthotopic heart transplantation more than 5 years previously and in a good circulatory condition.

The research results can be summarized as follows:
healthy subjects:
a) the autocorrelation function, estimated by analyzing the tacogram and the differences in windows of 1000 heartbeats, revealed great variability even in the same subject. We therefore analyzed windows with at least 10 000 beats, rejecting any artifact, in order to have a temporal mediate reading. The analysis results on the 15 subjects observed can be summarized as follows. The tacogram shows an autocorrelation function that does not reach zero during the 200 heartbeats. This trend can be interpreted both as evidence of short-term memory and as an effect of nonstationary state. We would prefer the second explanation on the basis of the analysis of the differences. Indeed it can be observed that, after a first area of about 20 beats in which the diagram is notably different from zero, it stabilized on values that are definitely near to zero within a 5/100 height band. This demonstrates that autocorrelation of the heartbeats in the tacogram carried out in the healthy subjects, is proof of existence of short-term memory. Specifically, this memory is somewhere around 20 heartbeats and, in all the subjects observed, it is however always below 40 beats. Taking this distance as a reference, we can also say that 2 beats at a greater distance do not correlate and that each beat influences the subsequent one at a shorter distance;
b) according to the window considered, the spectrum analysis of the tacogram shows one or two peaks, that is two periodic components: one with a frequency of 0.1 Hz and the other with a frequency of 0.3 Hz, called respectively low frequency and high frequency. These periodic elements are of little account if compared to the part of the spectrum close to null frequency. This phenomenon can be explained in two ways: either as an expression of chaos in the heart dynamics or, more easily, as a continuing nonstationary state in the window considered. In order to prove the latter hypothesis, we extended our analysis to cover the acceleration sequence. We could thus observe that the part of the spectrum with null frequency is virtually set to zero. We interpret

this phenomenon as the filtering of nonstationary elements rather than as the expression of minor chaos in the tacogram. The tacogram spectrum also shows a particularly marked 0.3 Hz frequency peak, acting as prevailing periodicity. It is to be remembered, however, that the importance to be given to an element depends on the ratio between the area bounded by the peak and the area of the whole spectrum. The latter is equal to the square of the standard deviation. At all frequencies, we have constantly observed a small element of the spectrum called white noise , which we interpreted as an expression of the random part of the beat. It is to be noted that, also in this situation, if a different window of the same tacogram is analyzed, the noise extent, the peak position and its height may change. This is due to the incomplete stationary state to which the different sequence is susceptible, which reflects the physiological changes that have taken place in the subjects. The results of our observations in the healthy subjects prove the existence of short-term memory in the heartbeat.

heart transplant patients:

a) the autocorrelation index shows that memory can be assessed in about 10 beats. As for the function variability dependent on the window observed, in these patients we noted the same behavior we observed in the healthy individuals, although the variability was slightly lower than in the latter group (Figs. 1 and 2);

b) the spectrum analysis of the tacogram diagrams and the results obtained in the transplanted patients are not basically different from those obtained in healthy subjects as can be observed in the diagrams reproduced (Figs. 3 and 4).

Drawing our conclusions from this research, we can say, on the basis of the results obtained, that heart s memory, interpreted as the residual information between one cardiac cycle and the subsequent one, is a very definite phenomenon (short-term memory) both in healthy subjects and in heart transplant recipients.

This memory effect, which we observed in previous research (limited by the autocorrelation), is now further confirmed by a more sophisticated study, such as the spectrum analysis of the values expressing heartbeat acceleration variability. With the spectrum analysis we observed in fact a periodical element that, beyond all doubt, indicates a memory effect.

This memory effect is presumably the result of the various and complex electrostatic modifications, in the jonic gradient, in the membrane permeability, in its

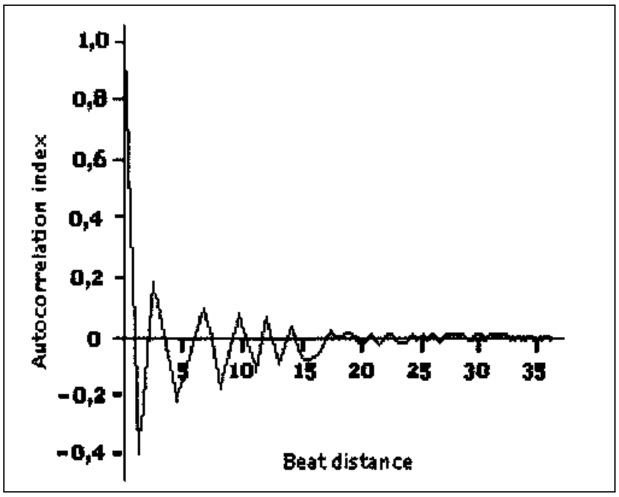

Figure 1. *Normal subject. Autocorrelation ind ex of the tachogram.*

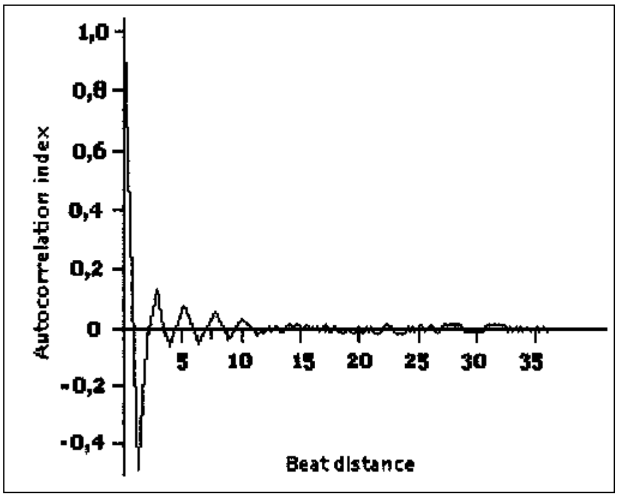

Figure 2. *Transplanted subject. Autocorrelation ind ex of the tachogram.*

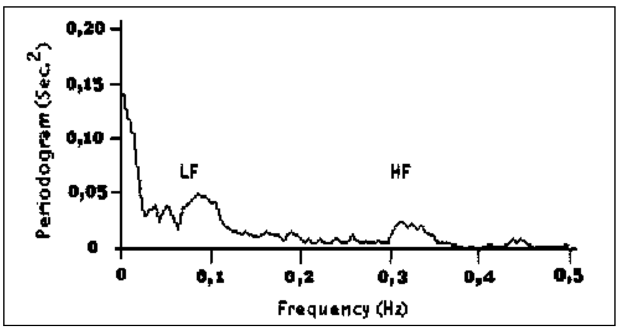

Figure 3. *Normal subject. Spectral analysis of the tachogram. HF = high frequency; LF = low frequency.*

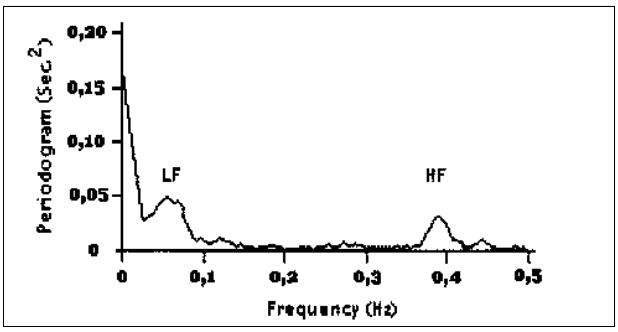

Figure 4. *Transplanted subject. Spectral analysis of the tachogram. Abbreviations as in figure 3.*

conducibility, etc., taking place in each heart muscle fiber when its kinetic activity starts. The complex dynamic network among sodium, potassium, calcium ions in the development of the action potential of membrane in the heart muscle fiber distinguishes this potential not only from the potential of all the other cell membranes of the body, but also from the potential of the skeletal myocyte. Furthermore, this action potential also differentiates itself in the heart muscle fiber where it can take both a quick and a slow form, both in different heart regions, for different muscle fibers and, for the same fibers, in different functional moments. A further breakthrough is the recent recognition that the regulation of the ionic canal function takes place by means of a variable genetic expression which can be demonstrated through altered synthesis of the membrane proteins. It is not unlikely that even small modifications in the G protein structure may affect the response of the myocardial kinetic activity to autonomic and autochthonous stimuli.

A substantiated memory effect in heart transplant patients is extremely significant. In these people, in fact the memory effect cannot be absolutely explained to interference or to the activity of the central and/or peripheral nervous system, as the transplanted heart is a denervated heart by definition. Moreover, this is indirectly confirmed by the morphological difference in the phase space, which in patients who underwent heart transplantation more than 5 years previously is not the same as in healthy subjects, and which has already been discussed. Moreover, an immediate regulating effect of hormone factors in the short-term heartbeat regulation is not completely plausible. As already known, the transplanted heart responds to an emergency situation autonomously and autochthonously in proportion to the signals reaching it directly from the circulation (vascular resistance, blood pressure, etc.). This implies the existence of functional memory that is likely to be inborn in the conduction system of the heart.

Beyond any doubt the identification of a memory effect in the cyclic activity of the heart shows the myocardial kinetic activity in a different perspective, not only at a physiological level but also at an arrhythmologic level. It is to be hoped that further clinical, mathematical and statistical studies will be extended to cover not only those rhythm disorders in which long-term memory is already recognized (intermittent left bundle branch block, Wolff-Parkinson-White syndrome, etc.), but also the most common arrhythmias and the different polymorphic manifestations of heart disease.

Looking at the results of our research we can conclude by quoting the aphorism that was the title of one of our recent publications: *cor ipse se reget, cor ipse se alit, cor ipse se movet* (it autonomously models itself on all the different modifications in the circulation, it feeds itself as the organ propelling blood circulation and, if necessary, it carries on its kinetic activity autonomously).

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