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Evaluation of autonomic imbalance in patients with heart failure: A preliminary study of pupillomotor function

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Abstract

Background: *Purpose of this study was to examine pupil size changes and mobility in normal subjects and in heart failure (HF) patients.*

Methods: *Sixteen stable patients with New York Heart Association (NYHA) class II or III heart failure and sixteen control subjects were studied. Pupillary reaction to light was recorded and nine parameters from this data were measured, reported and then compared in both groups of subjects.*

Results: *Patients with HF had abnormal pupillary function compared with normal subjects. Pupillary light reflex variables differed significantly between two groups ($p < 0.05$) except baseline radius (R1), minimum radius (R2) and time for maximum constriction (T3). A significant decrease in maximum constriction velocity (VCmax; $p < 0.001$) and maximum constriction acceleration (ACmax; $p < 0.001$) was observed in HF subjects. Furthermore, significantly higher values in percentage recovery-redilatation (%R; $p < 0.001$), percentage R2/R1 (%R2/R1; $p < 0.05$), latency (T1; $p < 0.05$) and time for maximum velocity (T2; $p < 0.05$) were found in the same group.*

Conclusions: *Of the parameters studied, R1 and %R are governed mainly by the action of the sympathetic nervous system, through norepinephrine. The rest are governed mainly by parasympathetic nervous system, through acetylcholine. The results of our study demonstrate generalized adrenergic activation and parasympathetic withdrawal, which are present in HF.* (Cardiol J 2010; 17, 1: 65–72)

Key words: pupil mobility, heart failure, adrenergic activation, pupillometry, prognosis

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Introduction

Heart failure (HF) is a principal complication of almost all forms of heart disease [1]. HF is defined as a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with, or eject, blood. The former is the classic form of systolic HF, while the latter is the diastolic HF (with preserved ejection fraction). The major symptoms of HF are dyspnoea and fatigue (which affect exercise ability) and fluid retention which may lead to pulmonary congestion and peripheral oedema.

It is estimated that 4.9 million people in the US are being treated for HF, with 550,000 new cases diagnosed each year. The prevalence of HF has dramatically increased over the past few decades as the population ages, with a mean age of the HF population being 74 years old [2]. The prognosis for HF is poor if the underlying condition cannot be rectified. HF has an enormous economic impact on health care systems and, despite the progress in medical treatment with beta-adrenergic blockers and angiotensin-converting enzyme inhibitors, mortality remains high [3–6].

The accuracy of diagnosis by clinical means alone is often inadequate, especially in women, elderly and obese. To access properly the prognosis and to optimize the treatment of HF, diagnostic dilemmas must be minimized. So, the introduction of additional markers that could evaluate disease progress in patients with HF and contribute to risk stratification is therefore of great significance [7, 8].

HF is characterized by generalized adrenergic activation and parasympathetic withdrawal [9, 10]. Under normal conditions, the inhibitory inputs from arterial and cardiopulmonary baroreceptor afferent nerves are the principal influence on sympathetic outflow. Parasympathetic control of heart rate is also under potent arterial baroreflex control. Efferent sympathetic traffic and arterial catecholamines are low, and heart rate variability is high. As HF progresses, the inhibitory input from arterial and cardiopulmonary receptors decreases and excitatory input increases. The net response to this altered balance includes a generalized increase in sympathetic nerve traffic, blunted parasympathetic and sympathetic control of heart rate and impairment of the reflex sympathetic regulation of vascular resistance [9]. Although there are no doubts about the importance of neuroendocrine mechanisms in the pathogenesis of HF, the role of neuroendocrine factors in diagnosis and prognosis is less clear. Plasma noradrenaline increases with age and healthy subjects over the age of 75 may have plasma concentrations of noradrenaline in the HF range [11].

Pupillometry is a simple, non-invasive technique that provides valuable data concerning the balance of both branches of autonomous nervous system [12–15]. Assessment of pupil reflex has previously been used in alcoholism [16], Down's syndrome [17], depression [18, 19], generalized anxiety disorder [20], drug abuse [21, 22], mental retardation [23], Alzheimer's disease [15, 24–30], and Parkinson's disease [31, 32].

Our aim in this study was to examine pupil size changes and mobility optically in HF patients and to identify simple markers that could be used in the diagnosis of HF and could accurately predict adverse events, especially death and hospitalization.

Methods

Study population

Heart failure patients. Sixteen patients were recruited from the cardiology ward of the 1st Department of Cardiology, AHEPA Hospital, Aristotle University of Thessaloniki, Greece. All were patients with symptomatic HF, New York Heart Association (NYHA) class II or III at optimal medical treatment, matching the Framingham criteria for the diagnosis of HF. The aetiology of HF was coronary artery disease in 12 cases and idiopathic dilated myocardiopathy in the other four. The diagnosis of HF was established by clinical evaluation and laboratory testing, using invasive and noninvasive tests including electrocardiography (ECG), chest roentgenogram, echocardiogram and coronary angiography as clinically indicated [7, 8, 33]. The mean age was 67.5 ± 11.2 and the mean left ventricular ejection fraction was 32 ± 0.06%.

Patients had visual acuity of 10/10 or corrected, and no history of ocular abnormalities or ocular trauma. Exclusion criteria were systemic conditions with known ocular involvement, systemic medication with known central nervous system effect, use of topical eye treatment and neurological or psychiatric illness.

Control subjects. Sixteen normal sedentary controls were selected on the basis that they were both age- and sex-matched with respect to the patients. They were all randomly selected among hospital staff, patients, relatives and visitors, and had no past medical history.

The whole study was conducted in the Laboratory of Clinical Neurophysiology in the Aristotle University of Thessaloniki, AHEPA Hospital, Thessaloniki, Greece. All subjects provided written informed consent and all experiments were approved

by the Ethical Committee of the AHEPA University Hospital based on the Helsinki Declaration. All subjects underwent standard blood and biochemical laboratory tests, and went through a full ophthalmological evaluation. All subjects were tested between 09:00 and 15:00.

Infrared pupillometry

Pupillary measurements were taken with a fully automated system which includes:

1. **A CCD high speed digital camera**: up to 262 frames per second with maximum sensitivity in the red and infra-red region of the spectrum.
2. **A computer** and the associated sampling cards.
3. **A light source:** two independent light sources are used in the system: a) an infra-red light source which illuminates the face of the person, consists of an array of 32 LEDs with 820 nm wavelength and is switched on permanently throughout the measurement and b) a clinical photic stimulator (SLE), made by Bio-logic Systems Corporation UK. A light flash is produced by a light bulb, through the discharge of a capacitor, with 20 ms duration.
4. **A traversing mechanism:** the whole instrument is based on an optical examination table with a head rest fixing the position of the head on one side. On the top of the table, the camera is fixed on a mechanism which can move in the three, x-y-z, directions. There is also a capability to rotate the camera on both the x-y and the x-z planes.
5. **Image processing analysis** which executes the calculations of the pupil reflex in real-time. The camera is capable of taking a maximum of 262 frames per second. The actual speed of the camera is controlled by the software developed for this purpose.

Because of the corneal curvature and, in order to avoid errors due to optical distortion, the camera was set normal to the axis of the eye and at a distance of 30 cm, so that the image of the pupil was symmetrical.

Experimental conditions

Subjects were asked to spend two minutes in the examination room to allow their pupils to adjust to the low lighting conditions. Each subject sat upright on a chair and rested their chin and forehead against the construction's special positions and fixated an infrared light in the same axis with the camera, at a distance of 1.5 m. Then five rectangular light flashes, with a 30 s interval, were administered.

The test was applied five times on each eye of each subject to test the repeatability and accuracy of the system. The duration of the stimulus was 20 ms and the luminance 24.6 candelas/m^2. In the interval of 30 s a full record is completed and in the same period we had to decide whether this record should be rejected or be saved if it was free of any artefacts. At the end of each measurement trial, a full record of the pupil's reaction radius and centre, as a function of time, was recorded and then analyzed online. From this data latency, velocity and acceleration were calculated, as well as other relevant parameters.

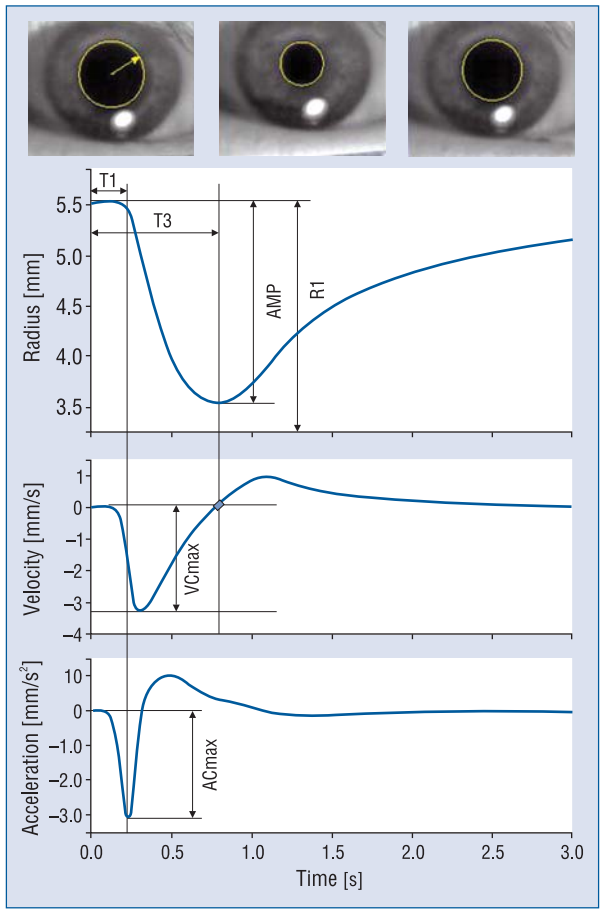

Figure 1. Pupil size after two minutes' dark adaptation before pupils' reaction to light, maximum constriction and redilation as response to light stimulus. Parameters measured: latency (T1), time for maximum velocity (T2), time for maximum constriction (T3), amplitude (AMP), baseline radius (R1), minimum radius (R2), maximum constriction velocity (VCmax), and maximum constriction acceleration (ACmax).

Parameters measured

Five artefact-free pupil response curves were easily obtained for each person. No one complained of discomfort and everyone was able to finish the test. Blinking necessitated repeating the test. Parameters measured were (Fig. 1): baseline pupil radius after

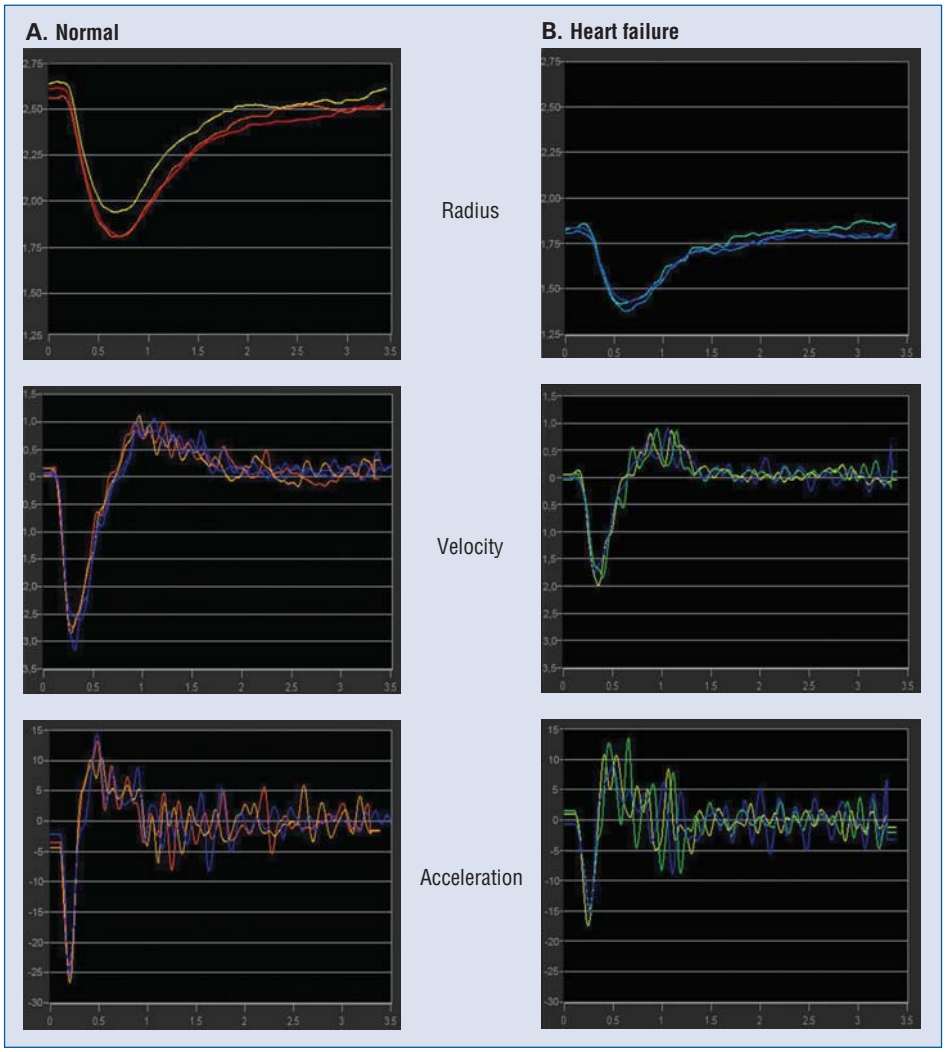

Figure 2. Typical pupil light reflex curve of a normal (**A**) and a heart failure patient (**B**) of matching age and gender. The difference in amplitude (AMP), maximum constriction velocity (VCmax), and maximum constriction acceleration (ACmax) is obvious between the two subjects.

two-minutes dark adaptation (R1); latency for the onset of constriction (T1); minimum pupil radius after pupil's reaction to light (R2); maximum constriction velocity (VCmax); maximum constriction acceleration (ACmax); time for maximum velocity (T2); time for maximum constriction [this is defined as the time when the constriction velocity is zero (T3)]; 3.5 s percentage recovery-redilatation (this is defined as the ratio of final pupil radius/baseline pupil radius at the end of the measurement which lasts 3.5 s — R%); R2/R1 ratio (R2/R1%).

The measurement and recording necessary to obtain the above parameters covered the changes to the size of the pupil for a period of 3.5 s from the application of the light flash.

Each measurement of total duration of 3.5 s corresponds to a full record of the reaction of the pupil, starting from the reduction of the diameter, the attainment of maximum miosis and the return to normal.

Radius measurement. The use of the radius instead of the diameter seems more reliable and appropriate. It can be used even when the upper lid covers part of the pupil and thus reduces the number of trials the researcher is obliged to drop. On the other hand, it is very easy to translate all data using radius to diameter: values are multiplied with the factor 'two'.

Statistical analysis

All statistical analyses were calculated according to the averaged measurements of five artefact-free pupillary light reflex (PLR) curves, of the right eye as no statistical difference was found between the two eyes ($p > 0.89$; Fig. 2) [37, 38]. PLR variables

Table 1. Pearson correlation of pupillary light reflex variables, overall and within normal and heart failure (HF) group.

	R2	%R	T1	T2	T3	VCmax	ACmax	%R2/R1
R1								
Normal	0.927**	0.444	0.178	0.512**	0.341	0.459	0.122	0.247
HF	0.971**	0.478	–0.296	–0.437	–0.602*	0.395	–0.505*	0.081
R2								
Normal		0.744**	0.010	0.331	0.497	0.225	0.192	0.517*
HF		0.671**	–0.245	–0.501*	–0.536*	0.407	–0.358	0.257
%R								
Normal			–0.321	–0.130	0.653**	–0.314	0.295	0.798**
HF			0.060	–0.449	–0.100	0.297	0.264	0.703**
T1								
Normal				0.111	–0.171	0.728**	0.236	–0.088
HF				0.207	0.021	0.182	0.172	0.123
T2								
Normal					–0.365	0.542*	–0.480	–0.417
HF					0.267	0.119	0.338	–0.410
T3								
Normal						–0.410	0.599*	0.499*
HF						–0.189	0.429	–0.022
VCmax								
Normal							–0.025	–0.191
HF							–0.019	–0.183
ACmax								
Normal								0.336
HF								0.439

*Correlation is significant at $p < 0.05$ level; **correlation is significant at $p < 0.01$ level; R1 — baseline pupil radius; R2 — minimum pupil radius; %R — 3.5 s percentage recovery-redilatation; T1 — latency; T2 — time for maximum velocity; T3 — time for maximum constriction; VCmax — maximum constriction velocity; ACmax — maximum constriction acceleration; %R2/R1 — R2/R1 ratio

were normally distributed and were summarized with means and standard deviations for both the normal and the HF group. The Pearson product moment correlation coefficient (r) was employed to calculate the relationships among all depended variables for the 32 subjects and for the normal and heart failure groups separately. The differences between the mean scores of the two groups for all the dependent variables were assessed with the t-test. In order to illustrate the classification and discrimination accuracy of the pupillary light reflexes, we also performed receiver operating characteristic (ROC) curve analyses. The area under the curve (AUC) of the ROC curves was estimated and used as the index of classification accuracy, where a variable with an AUC = 1 indicates perfect discrimination ability into HF or normal group, while a variable with an AUC near 0.5 indicates poor discrimination ability into the two groups. Analyses were conducted in SPSS 14 (SPSS Inc., Chicago, IL, USA).

Results

Correlations among all the PLR variables for the 32 subjects, and for the normal and HF patient groups separately, are listed in Table 1. Paired t-test analysis was then employed to examine the differences between the mean scores of the two matched groups for all PLR variables. This revealed significant differences between them for six out of nine PLR variables (Table 2). Specifically, the mean values of VCmax ($p < 0.001$) and ACmax ($p < 0.001$) were significantly lower in HF subjects compared to control subjects. Conversely, the mean scores of T1 ($p < 0.05$), T2 ($p < 0.05$), %R ($p < 0.001$) and %R2/R1 ($p < 0.05$) were significantly higher in the HF group compared to the control group. There was no significant difference between the two groups for R1, R2 and T3. Table 3 provides evidence of the classification power of the best PLR variable in discriminating the subjects of the two groups. ACmax was

Table 2. Descriptive statistics for pupillary light reflex variables for normal and heart failure groups.

	Normal (n = 16)				Heart failure (n = 16)				p*
	Min	Max	Mean	SD	Min	Max	Mean	SD	
R1	1.355	3.740	2.770	0.659	1.950	2.827	2.434	0.275	0.074
R2	0.931	2.881	2.020	0.559	1.460	2.415	1.981	0.295	0.808
%R	58.651	79.486	72.390	5.073	72.183	89.190	81.046	4.849	< 0.001
T1	0.200	0.265	0.233	0.018	0.208	0.272	0.249	0.021	0.030
T2	0.273	0.354	0.323	0.022	0.284	0.384	0.344	0.027	0.021
T3	0.712	0.773	0.740	0.023	0.740	0.860	0.740	0.078	0.990
VCmax	2.904	–2.032	–2.402	0.241	–2.095	–1.557	–1.825	0.175	< 0.001
ACmax	–32.087	–19.229	–24.601	3.356	–15.329	–12.480	–14.196	0.274	< 0.001
%R2/R1	81.164	97.443	93.960	4.107	95.470	99.850	97.486	1.292	0.004

*Paired t-test and $p < 0.05$ considered significant; R1 — baseline pupil radius; R2 — minimum pupil radius; %R — 3.5 s percentage recovery--redilation; T1 — latency; T2 — time for maximum velocity; T3 — time for maximum constriction; VCmax — maximum constriction velocity; ACmax — maximum constriction acceleration; %R2/R1 — R2/R1 ratio; SD — standard deviation

Table 3. Classification accuracy of pupillary light reflexes.

PLR	AUC	95% CI	p*
ACmax	1.000	1.000–1.000	< 0.001
VCmax	0.988	0.963–1.000	< 0.001
%R	0.906	0.807–1.000	< 0.001
%R2/R1	0.848	0.715–0.980	< 0.001
T2	0.768	0.594–0.941	0.010
T1	0.766	0.592–0.939	0.010
T3	0.553	0.326–0.780	0.611
R2	0.477	0.265–0.689	0.821
R1	0.297	0.107–0.487	0.005

*$p < 0.05$ considered significant; CI — confidence interval; PLR — pupillary light reflex; R1 — baseline pupil radius; R2 — minimum pupil radius; %R — 3.5 s percentage recovery-redilation; T1 — latency; T2 — time for maximum velocity; T3 — time for maximum constriction; VCmax — maximum constriction velocity; ACmax — maximum constriction acceleration; %R2/R1 — R2/R1 ratio; AUC — area under the curve

the best predictor in determining a subject to be a HF patient (AUC = 1) leaving VCmax in second place, with almost perfect classification ability (AUC = 0.998), and %R and %R2/R1 in third and fourth places, also with high classification ability (AUC = = 0.908 and AUC = 0.848, respectively). R1 and R2 were ranked last with a lower AUC, indicating poor classification power in discriminating between the two groups ($p = 0.05$ and $p = 0.821$, respectively). Figure 2 shows the average curves of VCmax, ACmax and R1 of the right eye in normal subjects and HF patients after two minutes' adaptation, before and after the pupils' reaction to light.

Discussion

To the best of our knowledge, this is the first study that has evaluated pupil size and mobility for the assessment of the autonomic nervous system in patients with HF. In this study, pupillometric measurements were taken by a standardized, fully automated, unique pupillometry system. The accuracy of this pupillometry system has successfully been proved in previous studies [37, 38]. The selection of patients who entered the study was strictly according to the inclusion and exclusion criteria; the control group was perfectly age- and sex--matched to the patient group. The examination conditions were identical for all subjects, adding to the reliability of the results of the present investigation.

Pupillometry is widely used to assess the balance of both branches of the autonomic nervous system (ANS), based on the fact that the size and reaction of the human pupil are under the antagonistic action of the parasympathetic nervous system (ParN) and the sympathetic nervous system (SNS) [24]. Furthermore, in the absence of a documented peripheral disorder of the ANS, pupil size reflects the integrated output of the sympathetic and parasympathetic pathways. The cardiac sympathetic nerves are preferentially stimulated in severe HF, with Nor release from the failing heart at rest in untreated patients increased up to 50-fold, which is similar to the levels of release in healthy hearts during near-maximal exercise [34].

The precision of results is significantly higher for latency, velocity and acceleration when a sam-

pling rate of 300 frames/s is used, when the experimental procedure is repeated at least four times, and when the results are averaged [39]. This high sampling rate was also used in our study (263 frames/s), and the average of five flash measurements was calculated. In view of the strict selection of subjects (normal and HF patients), as well as the method used, our results may be considered reliable.

In accordance with the central nervous system integratory mechanisms that govern the PLR, the characteristic V-shaped response is divided into three segments: a primary that is due exclusively to ParNS excitation; a middle that is attributed both to the SNS and the ParNS; and a latter that reflects only SNS activity [35]. Thus it is evident that the parameters involved in the first segment, especially ACmax and VCmax, are extremely sensitive indicators of cholinergic activity. On the other hand, the resting pupil diameter is mainly under sympathetic control and the diameter reduction is a sign of diminished sympathetic outflow to the iris muscles [36]. Additionally, the most sensitive indicator of SNS activity resides in the third segment of the V-shaped response. Thus %R can be used as an indicator of SNS activity [35].

In our study, HF patients had significantly lower levels of VCmax and ACmax compared with normal subjects. Conversely, HF patients had significantly higher levels of %R, T1, T2, %R2/R1 compared with normal subjects. There was no significant difference between the two groups for R1, R2 and T3. The low levels of ACmax and VCmax indicate a cholinergic deficit in HF derived from a blunted parasympathetic system. The high levels of %R2/R1, and especially %R, are indicative of an increased adrenergic activity with increased levels of circulating norepinephrine. Another very important observation is that ACmax was the best predictor in classifying a subject as HF or normal.

Limitation of the study

Pupillometry cannot be used in patients suffering from retinopathy or other ophthalmological, psychiatric or neurological diseases, because pupil mobility may be affected and lead to false conclusions.

A low percentage of our patients were under treatment with beta-blockers that could possibly interfere with pupil size and mobility. However, we know of no reference currently available concerning the possible effect of the systematic use of such medication on pupil size and mobility.

The size of our sample is small but the statistically significant difference allows us to draw early conclusions. This is the first study ever that has used pupil size changes and mobility to evaluate autonomic imbalance in patients with HF. However, this is only a preliminary report and further studies are encouraged to replicate the above findings.

Conclusions

All parameters analyzed here, except baseline pupil radius (R1), minimum pupil radius (R2) and time for maximum constriction (T3) revealed statistically significant differences between HF patients and normal subjects. This is an indication of abnormal pupillary function in HF patients compared with healthy subjects. However, the most important finding is that ACmax is the best predictor of subject classification as normal or HF.

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