that the circadian temperature rhythm persisted without damping during the circabidian period.

Parts of the sleep-wake pattern observed in the present subjects are regarded as the circabidian rhythm. In subject A, the mean circabidian period of sleep-wake cycle was 48 h and 50 min from day 3 to day 8, and 49 h and 50 min from day 9 to day 11, while the body temperature rhythm kept a circadian period. In subject B, the circabidian rhythm persisted for only one cycle with two long sleep episodes with a short nap in between, and had a period of 49 h and 50 min. The circabidian rhythm in subject A appeared spontaneously the first time, and the second time on the day following the light pulse. The first circabidian rhythm disappeared after the light pulse, but the second one was replaced by the circadian rhythm without any recognizable trigger. The circabidian rhythm in subject B appeared on the day following the light pulse and disappeared spontaneously.

It is not known whether or not there is a causal relation between bright light and the circabidian rhythm. The vicissitude of the circabidian rhythm observed in association with the light pulse might be an accidental coincidence. However, it is possible to relate the appearance and disappearance of the circabidian rhythm to the bright light pulse. The bright light pulse phase-advanced the free-running human circadian rhythms when it was applied early in the subjective day, and slightly phase-delayed them when applied late in the subjective day[9]. In addition to the phase shift, Czeisler et al.[10] reported that bright light changes the amplitude of the circadian rhythm in rectal temperature. On the other hand, Daan et al.[11] predicted in their two-process model that the change in the amplitude of the circadian oscillation (represented by the circadian temperature rhythm) will produce a circabidian period in the sleep-wake cycle. Taking these together, it is tempting to speculate that the bright light pulse changes the amplitude of the circabidian rhythm. Alternatively, the bright light pulse may change the threshold for sleep, which is also a possible cause of the circabidian rhythm in the two-process model[11].

The circabidian rhythm in mood has been reported in psychiatric disorders, especially in manic-depressives[12–14]. Recently, bright light therapies have been introduced in the treatment of a certain type of depression[15]. The pathophysiology of why bright light is beneficial is a matter of debate, but it seems to be generally accepted that an abrupt change in the circadian system is related to the improvement of the illness[16]. This is also suggestive of a causal relationship between the bright light pulse and the circabidian rhythm.

Of course, it is premature to draw any conclusion from the present two cases on the causal relation between bright light and the circabidian rhythm. However, the findings obtained here may provide some insight into the mechanism of the circabidian rhythm.

Acknowledgment. This work was supported in part by grants from the Ministry of Education, Science and Culture of Japan (No. 62304044), the Hokkaido Prefectural Government, and the Akiyama Foundation.

1 Colin, J., Timbal, J.,Boutelier, C., Houdas, Y., and Siffre, M., J. appl. Physiol. *25* (1968) 170.
2 Jouvet, M., Mouret, J., Chouvet, G., and Siffre, M., in: The Neurosciences, Third Study Program, p. 491. Eds F. O. Schmitt and F. G. Worden. The MIT Press, Massachusetts, 1974.
3 Mills, J. N., Minors, D. S., and Waterhouse, J. M., J. Physiol, Lond. *240* (1974) 567.
4 Aschoff, J., Gerecke, U., and Wever, R., Jap. J. Physiol. *17* (1967) 450.
5 Wever, R. A., The Circadian System of Man. Springer-Verlag, New York 1979.
6 Wever, R. A., Ann. N. Y. Acad. Sci. *453* (1985) 282.
7 Czeisler, C. A., Allan, J. S., Strogatz, S. H., Ronda, J. M., Sanchez, R., Rios, C. D., Freitag, W. O., Richardson, G. S., and Kronauer, R. E., Science *233* (1986) 667.
8 Honma, K., Honma, S., and Wada, T., Experientia *43* (1987) 572.
9 Honma, K., Honma, S., and Wada, T., Experientia *43* (1987) 1205.
10 Czeisler, C. A., Allan, J. S., Kronauer, R. E., Abstracts of 5th ICSR, Copenhagen, 1987, p. 15.
11 Daan, S., Beersma, D. G. M., and Borbély, A. A., Am. J. Physiol. *246* (1984) R161.
12 Gelenberg, A. J., Klerman, G. L., Hartmann, E. L., and Salt, P., Br. J. Psychiat. *133* (1978) 123.
13 Paschalis, C., Pavlou, A., and Papadimitrious, A., Br. J. Psychiat. *137* (1980) 332.
14 Welsh, D. K., Nion-Murcia, G., Gander, P. H., Keenan, S., and Dement, C., Biol. Psychiat. *21* (1986) 527.
15 Rosenthal, N. E., Sack, D. A., Gillin, J. C., Lewy, A. J., Goodwin, F. K., Davenport, Y., Mueller, P. S., Newsome, D. A., and Wehr, T. A., Archs gen. Psychiat. *41* (1984) 72.
16 Wirz-Justice, A., Schmid, A. C., Graw, P., Krauchi, K., Kielholz, P., Poldinger, W., Fisch, H.-U., and Buddenberg, C., Experientia *43* (1987) 574.

0014-4754/88/11-120981-03$1.50 + 0.20/0

Nonlinear dynamics in sudden cardiac death syndrome: Heartrate oscillations and bifurcations

A. L. Goldberger[a], D. R. Rigney[a, c], J. Mietus[a], E. M. Antman[b] and S. Greenwald[c]

[a] *Cardiovascular Division, Beth Israel Hospital & Harvard Medical School, 330 Brookline Avenue, Boston (Massachusetts 02215),* [b] *Cardiovascular Division, Brigham and Women's Hospital & Harvard Medical School, Boston (Massachusetts 02115), and* [c] *Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge (Massachusetts 02139, USA)*

Received 9 February 1988; accepted 12 July 1988

Summary. Patients at high risk of sudden cardiac death show evidence of nonlinear heartrate dynamics, including abrupt spectral changes (bifurcations) and sustained low frequency (.01–.04 Hz) oscillations in heartrate.

Key words. Autonomic nervous system; electrocardiography; fractals; heart failure; nonlinear dynamics; ventricular fibrillation; ventricular tachycardia.

In the United States, sudden cardiac death is the leading cause of death among men aged 20–60 years[1]. We proposed[2–5] that nonlinear dynamics, a new branch of the basic sciences devoted to the mathematical analysis of complex systems, could be used to interpret the fluctuations in heartrate associated with the electrical instability exhibited

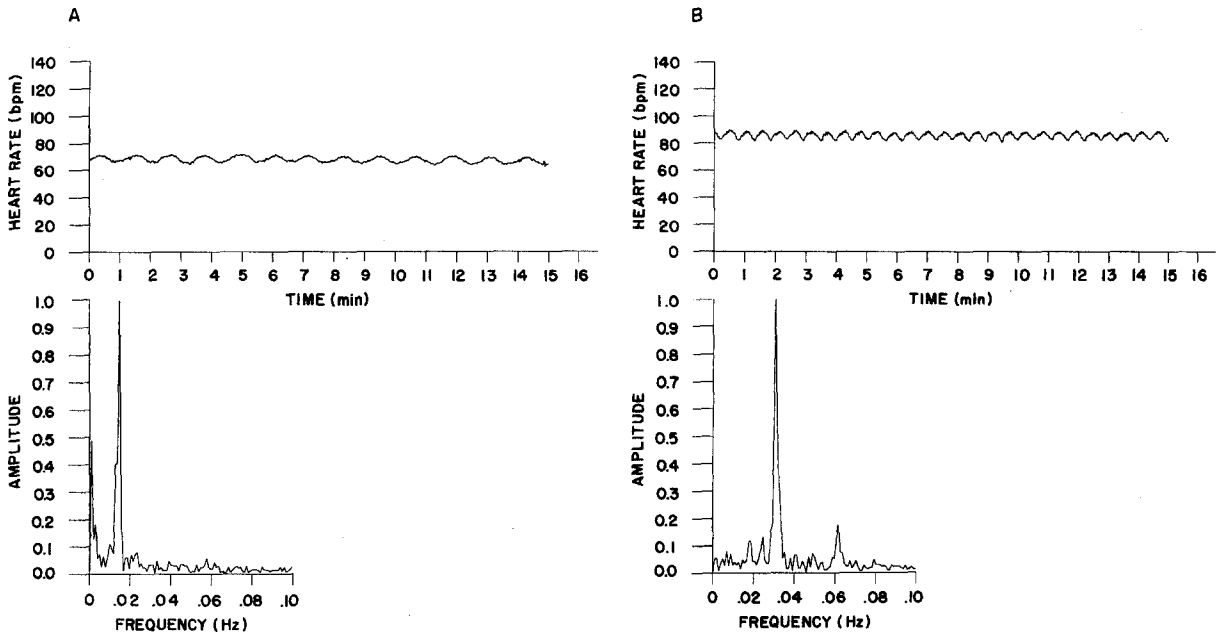

Figure 1. Heartrate time series (top) and frequency spectrum (bottom panel) are shown for two patients with severe congestive heart failure. Example *A* shows prominent heartrate oscillations with a single sharp spectral peak at 0.02 Hz. Example *B* shows an oscillatory pattern with a sharp spectral peak at about 0.03 Hz and a higher harmonic at about 0.06 Hz. Spectra for this and the following figures were obtained as follows. The instantaneous heartrate was obtained by interpolating the reciprocals of the nearest R–R intervals. The heartrate so obtained was sampled at 0.5-s-intervals and was then subjected to a Fast Fourier Transform.

by patients at high risk of sudden death. This brief report presents preliminary documentation of the types of nonlinear heartrate dynamics seen in such patients*.

We retrospectively performed a time series and Fast Fourier transform analysis of heartrate data from 16 patients in sinus rhythm (age range: 35–82 years) who had undergone Holter (ambulatory) electrocardiographic monitoring and who experienced one or more sustained episodes of a ventricular tachyarrhythmia during the recording. Each episode either ended with *cardiac arrest* or lasted for more than 30 s, and it consisted of either ventricular fibrillation or ventricular tachycardia. For comparison, we performed the same type of analysis on ambulatory ECG records of 14 patients (age range: 40–73 years) in sinus rhythm with severe congestive heart failure, a group that is known to be at high risk of sudden death[1]. This latter group was undergoing conventional medical therapy prior to receiving an investigational cardiotonic drug[6]. It included five patients who survived more than 2 years after the recording, five who died within 3 months due to progressive heart failure and four who died suddenly (8 days, 36 days, 53 days, and 208 days) following the recording (presumably from an arrhythmia).

The heartbeat time series and spectra from both groups were remarkably similar and exhibited the following basic patterns: 1) Low frequency sinus rhythm *heartrate oscillations*, which started and stopped abruptly. The Fourier spectrum of heartrate showed either a single frequency peak or a dominant peak with one or more harmonics (figs 1–3). Furthermore, in one patient, an apparent *subharmonic bifurcation sequence* was observed with an abrupt change from an oscillatory sinus rhythm pattern having a spectral peak at 0.04 Hz to one with a large peak at 0.02 Hz (fig. 2).

2) A *flat spectral pattern* (for frequencies up to about 0.1 Hz) associated with a marked diminution in physiologic beat-to-beat heartrate variability (fig. 4).

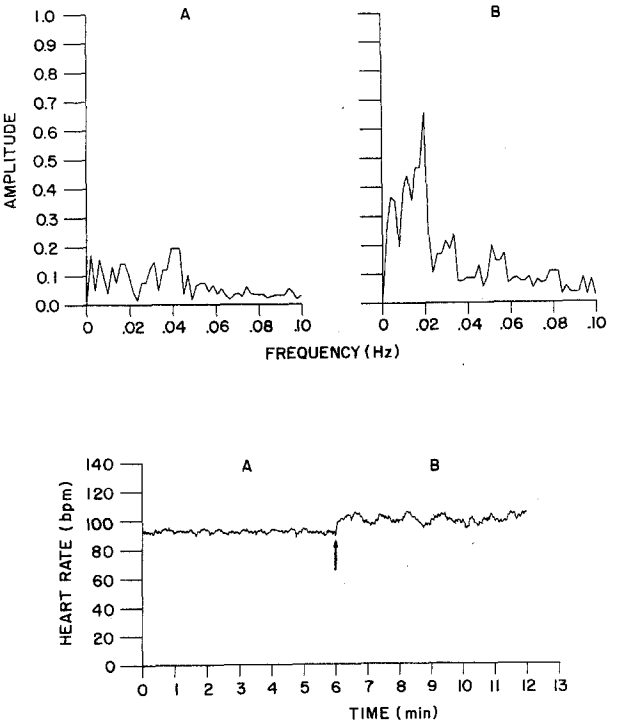

Figure 2. Heartrate time series from one of the patients with severe heart failure showed an abrupt spectral change associated with an increase in heart rate (arrow). Frequency spectrum for the first part of the recording (*A*) shows a dominant spectral peak at about 0.04 Hz. The frequency spectrum for the second part (*B*) shows a dominant peak at 0.02 Hz. This appears to be a *subharmonic bifurcation* (period-doubling) sequence, which is exhibited by a variety of perturbed nonlinear systems[3,11–14].

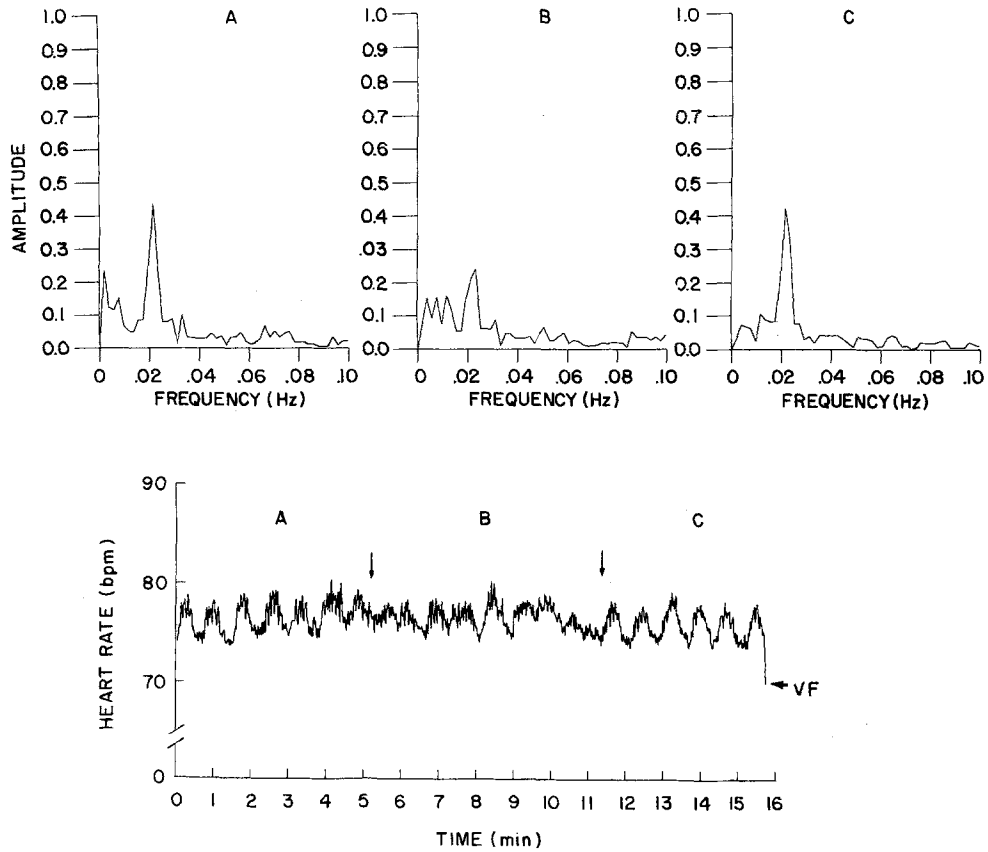

Figure 3. Heartrate time series and corresponding spectra for a patient who had a cardiac arrest due to ventricular fibrillation (VF) during the recording. Sections *A*, *B*, and *C* all show low frequency oscillations at about 0.02 Hz. Note the abrupt change in spectral amplitude during section B, with bifurcations indicated by vertical arrows.

The Holter records were scored in their entirety in 15-min blocks by three independent observers. Tape segments were classified as either oscillatory or flat only if there was agreement among all three observers. One or both of these patterns was noted in 14 of the 16 patients who actually experienced a life-threatening tachyarrhythmia during the recording and in all but one of the 14 patients with severe congestive heart failure.

Oscillatory dynamics were noted in a total of 23 of the 30 patients. The oscillations were primarily in the frequency band between 0.01 and 0.04 Hz, although lower and higher frequency oscillations (0.005 to 0.06 Hz) were also noted. In individual subjects, the frequency of the oscillations sometimes varied during the course of the recording. The oscillations lasted from minutes to hours. Among all the observed episodes of oscillations, the mean duration ($\pm$SD) was 37.1 $\pm$ 28.1 min, with a range of 6–225 min. Of these 23 patients, oscillations were present during 1–24% of the recording in 14 subjects, during 25–49% of the recording in 5 subjects, during 50–74% of the recording in 4 subjects, and during 75–100% of the recording in 0 subjects.

The flat spectral pattern was noted in a total of 21 of the 30 patients. Among all the observed episodes of a flat pattern, the mean duration ($\pm$SD) was 81.9 $\pm$ 114.2 min, with a range of 15–645 min. Of these 21 patients, the flat pattern was present during 1–24% of the recording in 9 subjects, during 25–49% of the recording in 3 subjects, during 50–74% of the recording in 5 subjects and during 75–100% of the recording in 4 subjects.

These findings are noteworthy because the spectra noted above are abnormal. Healthy subjects show considerable beat-to-beat sinus rhythm fluctuations[4,7]. The frequency

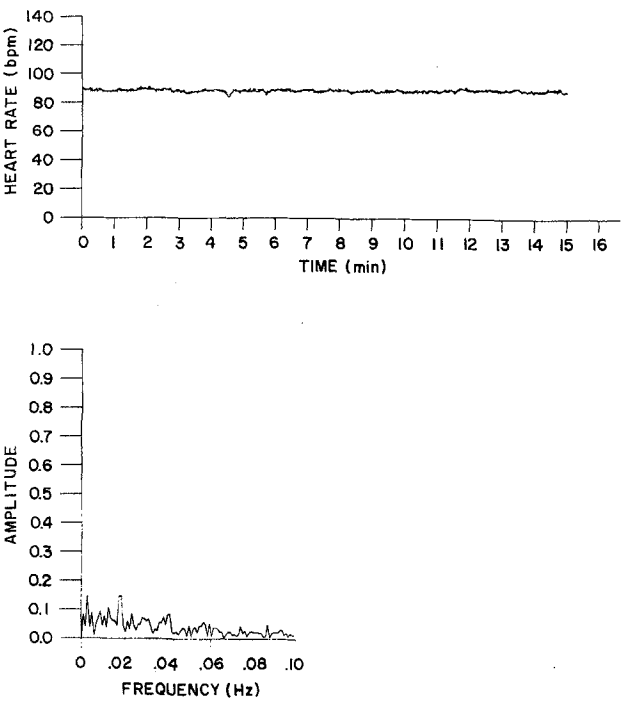

Figure 4. The heartrate time series (upper panel) shown in this patient, who developed ventricular fibrillation 11 h later, is characterized by the virtual absence of normal beat-to-beat heartrate variability. The spectrum (lower panel) is essentially flat, with a possible very low amplitude peak at about 0.02 Hz.

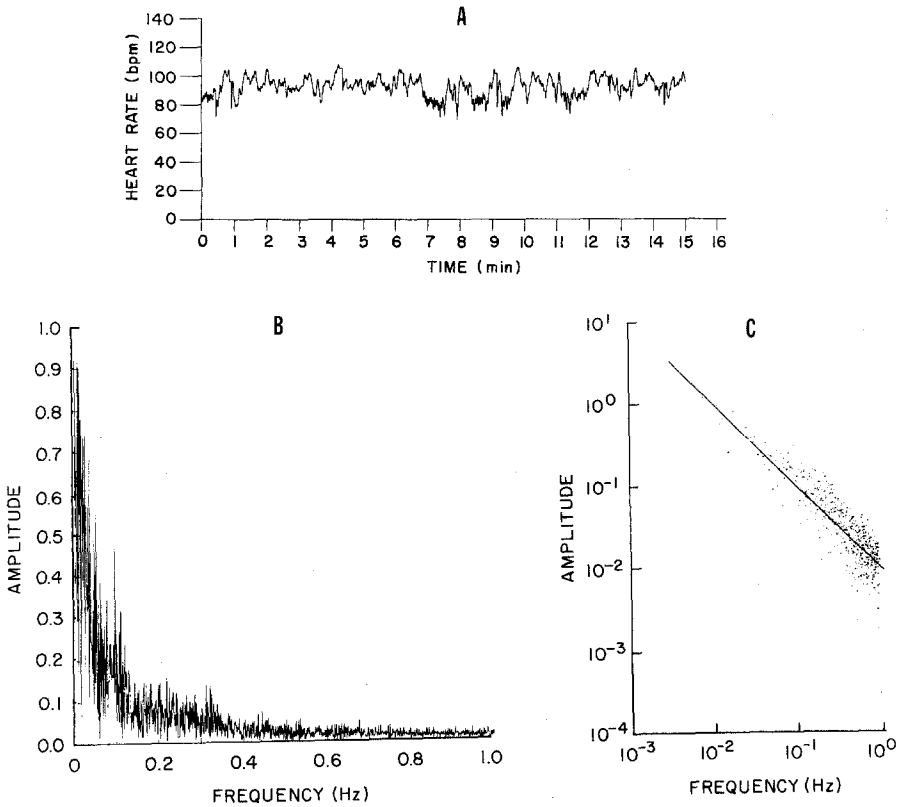

Figure 5. Healthy subjects show considerable beat-to-beat heartrate variability (*A*), represented by a broadband frequency spectrum (*B*), with a 1/f-like distribution (*C*). The graph in *C* was obtained by replotting the data in *B* on double log axes on which an inverse power-law (1/f-like) spectrum will appear as a straight line with negative slope. The slope obtained by linear regression was −1.005 in this case. This kind of broadband spectrum may be the consequence of a fractal control mechanism[3,4]. The pathologic spectral patterns shown in figs 1–4 are qualitatively different from this normal pattern and cannot be fit well to a 1/f-like distribution. In other pathological cases, including some patients with heart failure, the 1/f-like distribution may be preserved but with a more negative slope than normal[3,23].

spectrum of normal variations is broadband with a 1/f-like (inverse power-law) distribution and with superimposed peaks corresponding to physiologic oscillations that are due to respiration, baroreceptor control, thermoregulation and the renin-angiotensin system[4,7–10]. A representative example is shown in figure 5.

The mechanisms underlying the physiologic 1/f-like pattern and the periodic pathological patterns reported here are not known. We have proposed that physiologic heartrate variability is the result of neuroautonomic feedback by a nonlinear *fractal* system that gives rise to self-similar fluctuations over multiple scales of time[4,5,10]. The spectrum of such a process will be broad with a 1/f-like distribution.

In addition to the 1/f-like nature of the normal spectrum, two features in the abnormal heartrate data may be taken as evidence that the underlying dynamics in diseases as well as health are due to nonlinear mechanisms: 1) abrupt spectral changes (bifurcations) and 2) sustained oscillations. A particular type of abrupt change noted in several apparently unrelated nonlinear systems is illustrated in figure 2. In that example the oscillatory frequency of the heartrate suddenly halves, as some parameter of the system – in this case, apparently mean heartrate – is varied over a critical range. This *subharmonic bifurcation* phenomenon has been noted in a number of other situations in which cardiovascular dynamics are perturbed[3,11–14]. The sustained (non-damped) character of the oscillations is also important in identifying the underlying dynamics as being nonlinear in character. Low frequency (~.02 Hz) heartrate oscillations such as those reported here have been shown previously to correlate with oscillations in breathing amplitude (Cheyne-Stokes respiration)[2]. Periodic breathing of this type is common in patients with heart failure and may be initiated by circulatory delay[15,16]. However, it is not clear whether the heartrate oscillations accompanying Cheyne-Stokes physiology are due to entrainment of cardiac activity by respiration or to entrainment of both respiratory and cardiac dynamics to some central oscillatory mechanism[2].

The present report of cardiac dynamics in adults at high risk of sudden death complements previous reports that document the loss of heartrate variability prior to cardiac arrest during Holter monitoring[17], as well as in high risk patients following acute myocardial infarction[18]. Loss of heartrate variability and relatively low frequency heartrate oscillations have also been described in the fetal distress syndrome[19]. If there is a common mechanism among these examples, it may be a central or peripheral dysfunction of the autonomic nervous system[4]. What is the relationship between this autonomic dysfunction and sudden cardiac death due to ventricular tachyarrhythmia? Several links may be hypothesized. Low cardiac output states cause increases in sympathetic tone and reduction in parasympathetic tone that could simultaneously reduce heartrate variability and lower the threshold for ventricular fibrillation[18,20]. Furthermore, oscillations in heartrate may be associated with oscillatory fluctuations in metabolic or biochemical parameters (blood gases, electrolytes, autonomic tone) that could also destabilize His-Purkinje or myocardial cell membranes, predisposing to sustained ventricular arrhythmias. Alternatively, these heartrate dynamics may not be causally linked to risk of

sudden death but may only be an indirect consequence of other primary factors (low cardiac output, myocardial damage) that lead to electrical instability.

It is also conceivable that the observed alterations in heartrate variability are due to the fact that the subjects were taking pharmacological agents that could modify heartrate or autonomic regulation, independent of disease. We have no way of testing this hypothesis since we do not have Holter recordings of these patients prior to their treatment with drugs. The effects of pharmacological agents on the heartrate of patients at high risk for sudden death needs to be characterized, but we do not think it is likely that the drugs themselves are responsible for the observed heartrate variability. This is because the subjects were taking a variety of drugs (digitalis, diuretics, vasodilators, antiarrhythmic drugs), and one would have to postulate that any of them could produce the same type of heartrate patterns.

The observation of bifurcation behavior and sustained periodic heartrate dynamics has potential diagnostic and prognostic importance. Conventional diagnostic analysis of ambulatory heartrate data is usually limited to description of the mean heartrate and range, and to counts of the number of and morphology of abnormal (ectopic) beats. Time series and spectral analysis of these same records, however, clearly show that different runs of sinus rhythm are not necessarily equivalent. For example, one subject may show physiological heartrate variability with a broad, 1/f-like spectrum. Another with nearly identical heart rate mean and variance may show oscillations and bifurcations reflecting an instability in cardiovascular control [3 – 5]. Furthermore, apparently erratic ectopic beats may actually follow a periodic bursting pattern that is detectable only with time series analysis of long heartbeat data sets [21, 22], rather than appearing at random time intervals.

Finally, these preliminary observations of complex heartrate phenomena emphasize the need to construct nonlinear mathematical models to provide testable explanations for physiologic heartrate fluctuations. A mechanistic explanation for the 1/f-like heartrate spectrum in healthy subjects as well as the bifurcation behavior and the periodic dynamics associated with perturbations in cardiovascular control parameters seen in high risk patients should be provided by a unified model of the cardiovascular system and its autonomic control.

Acknowledgment. This research was supported in part by grants from the Whitaker Health Sciences Fund and the G. Harold and Leila Y. Mathers Charitable Foundation.

* This work was presented in part at the 32nd Annual Meeting of the Biophysical Society (28 February–4 March 1988, Phoenix, Arizona) and abstracted in Biophys. J. *53* (part 2) (1988) 399a.

1 Willerson, J. T., in: Cecil Textbook of Medicine, 16th edn., p. 256. Eds J. B. Wyngaarden, and L. H. Smith Jr. W. B. Saunders Co., Philadelphia 1982.
2 Goldberger, A. L., Findley, L. J., Blackburn, M. J., and Mandell, A. J., Am. Heart J. *107* (1984) 612.
3 Goldberger, A. L., and West, B. J., Ann. N. Y. Acad. Sci. *504* (1987) 195.
4 Goldberger, A. L., and West, B. J., Yale J. biol. Med. *60* (1987) 421.
5 Goldberger, A. L., and Rigney, D. R., Proc. Ninth Ann. Cong. IEEE Eng. med. Biol. Soc. *1* (1987) 313.
6 Baim, D. S., Colucci, W. S., Monrad, E. S., et al. J. Am. Coll. Cardiol. *7* (1986) 661.
7 Sayers, B. McA., Ergonomics *16* (1973) 17.
8 Kitney, R. I., and Rompelman, O., Eds, The Study of Heart Rate Variability. Clarendon Press, Oxford 1980.
9 Akselrod, S., Gordon, D., Shannon, D., et al. Science *213* (1981) 220.
10 Kobayashi, M., and Musha, T., 1/f fluctuation of heartbeat period. IEEE Trans. Biomed. Eng. *29* (1982) 456.
11 Guevara, M. R., Glass, L., and Shrier, A., Science *214* (1981) 1350.
12 Goldberger, A. L., Bhargava, V., West, B. J., and Mandell, A. J., Physica *17D* (1985) 207.
13 Ritzenberg, A. L., Adam, D. R., and Cohen, R. J., Nature *307* (1984) 159.
14 Goldberger, A. L., Shabetai, R., Bhargava, V., et al. Am. Heart J. *107* (1984) 1297.
15 Guyton, A. C., Crowell, J. W., and Moore, J. W., Am. J. Physiol. *187* (1956) 395.
16 Mackey, M. C., and Glass, L., Science *197* (1977) 287.
17 Martin, G. J., Magid, N. M., Myers, G., et al. Am. J. Cardiol. *60* (1987) 86.
18 Klieger, R. E., Miller, J. P., Bigger, J. T. Jr, et al. Am. J. Cardiol. *59* (1987) 265.
19 Freeman, R. K., and Garite, T. J., Fetal Heart Rate Monitoring, pp. 7–18, 89–112. Williams & Wilkins, Baltimore 1981.
20 Kolman, B. S., Verrier, R. L., and Lown, B., Am. J. Cardiol. *37* (1975) 1041.
21 Findley, L. J., Blackburn, M. R., Goldberger, A. L., and Mandell, A. J., Am. Rev. respir. Dis. *130* (1984) 937.
22 Glass, L. Goldberger, A. L., Courtemanche, M., and Shrier, A. Proc. R. Soc. Lond. A *413* (1987) 9.
23 Saul, J. P., personal communication.

0014-4754/88/11-120983-05$1.50 + 0.20/0

Chloride transport in the freshwater protozoan *Tetrahymena pyriformis*

F. Jessen and B. Kramhøft

Institute of Biological Chemistry A, University of Copenhagen, Universitetsparken 13, DK-2100 Copenhagen Ø (Denmark)
Received 11 July 1988; accepted 18 August 1988

Summary. Tetrahymena accumulates $^{36}Cl^-$ in both nutrient and salt media. Up to 80% of the initial net $^{36}Cl^-$ influx was inhibited by the anion exchange inhibitor DIDS (4,4'-diisothiocyano-2,2'-stilbene-disulfonic acid). The 'loop' diuretic, bumetanide, had no effect. A DIDS-sensitive anion exchange system is proposed to regulate the cytoplasmic Cl^- concentration in *Tetrahymena*.
Key words. Tetrahymena; anion exchange; DIDS; chloride transport; ion concentrations.