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Improving Pharmacotherapy of Arrhythmias in Childhood with Monitoring of Heart Rate Variability

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ABSTRACT

The pharmacotherapy of children with heart disease is uncertain because the necessary prospective studies are not being carried out. Until adequate clinical trials are not performed, pharmacotherapy in infants with heart disease should be evaluated using valid surrogate parameters. We use HRV monitoring of heart rate variability (HRV) to measure the effect of pharmacotherapy on the autonomic nervous system.

Methods: The children are routinely monitored with Dräger Infinity Monitors™ (Dräger; Germany) on the pediatric intensive care unit in life threatening arrhythmias or Holter ECG's during longtime follow up. For analysis of heart rate variability, we export the data to the Pathfinder™ ECG Software using a network connection. 10 clinical cases are discussed.

Results: Infants with life threatening tachycardia has low HRV probably induced by heart failure, indicated by elevated NT-Pro BNP and troponin T values. We report about two cases with a life-threatening amiodarone induced cardiovascular collapse. Furthermore, two children with sustained ventricular tachycardia got a treatment with propranolol.

Conclusion: Reduced HRV seems to be an important risk factor for life threatening complications in infants with arrhythmias. An improvement of HRV during pharmacotherapy seems to be important for longtime prognosis.

Keywords: Heart rate variability, Arrhythmias, Heart failure, Omega-3-fatty acid, Amiodarone collapse

INTRODUCTION

The pharmacotherapy of children with heart disease is not well evaluated because urgently required prospective studies are not being carried out so far. Until adequate clinical trials are not performed, pharmacotherapy in infants with heart disease should be evaluated using valid surrogate parameters. We are using heart rate variability (HRV) analysis with 24 h Holter ECG's to for pharmacotherapy monitoring in children with heart disease for the last 22 years. In contrast to biochemical parameters, the HRV analysis needs no painful blood sampling, is linked with low costs and admits immediate available results.

We have published a case collection, showing the improvement of pharmacotherapy in infants with severe heart failure by using an online monitoring of heart rate variability (HRV) [1]. We now publish the data of HRV monitoring in 10 children with life threatening arrhythmias [2].

Recently, it has been also shown that HRV monitoring is associated with improved prognosis in very low birthweight patients [3].

MONITORING

We are aware that pharmacotherapy in these high-risk infants demands for a close monitoring of the autonomic nervous system [4]. Starting with blood tests for renin and norepinephrine levels up to 2003, after 2005 we have used NT-Pro-BNP measurements for monitoring in heart failure. Beginning in 1998 we additionally used heart rate variability (HRV) monitoring with Holter ECG's [5]. Currently we additionally use online HRV monitoring in these infants on our pediatric intensive care unit (PICU), using a network connection between our Infinity Monitors™ (Dräger; Germany) with the Pathfinder™ Holter ECG Software (Spacelab; Germany).

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For this publication we select 10 cases, demonstrating the effect of pharmacotherapy on the autonomic nervous system.

METHODS

Subjects

Processing and analysis of 24 h-Holter recordings: The infants are routinely monitored with our Dräger Infinity Monitors™ (Dräger; Germany) in our pediatric intensive care unit. For analysis of heart rate variability, we exported the monitor data to the Pathfinder™ ECG Software using a network connection. All Holter recordings were reviewed by an experienced cardiologist and were edited to validate the system's QRS labeling in order to exclude artifacts. Measures of HRV were calculated employing only normal to normal intervals. The Holter ECG's were analyzed as average values from the entire 24 h of analyzable data. For this publication, we used frequency domain measures if the time domain measures have very low values in neonates and cannot differentiate the changes of the autonomic tone.

For time domain measures, mean RR interval, resulting heart rate and the following HRV parameters were calculated.

1) **Heart rate:** The easiest but very important HRV parameter is the average sinus rhythm heart rate, since all other parameters are significantly affected by the heart rate. The circadian heart rate difference was calculated by the subtraction of the mean heart rate at night from the mean heart rate at day.

2) **SDNN:** Standard deviation of all normal RR intervals in a time frame. This global HRV parameter represents the overall variability of the autonomic nervous system.

3) **rMSSD:** Square root of the arithmetic mean of the squared deviation of successive normal RR intervals in a time frame. This parameter is mainly influenced by the parasympathetic nervous system.

Frequency domain measures: Measurement and physiological interpretation of HRV parameters were performed according to the standards of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (5). Beat-to-beat fluctuations were transformed to the frequency domain using Fast Fourier Transformation. Spectral power was determined over three frequency regions of interest: very low frequency power (VLF, 0.004 - 0.04 Hz), low frequency power (LF, 0.04-0.15 Hz) and high frequency ipower (HF, 0.15 - 0.4 Hz). High frequency power reflects mostly vagal tone.

RESULTS

Case 1 (Figure 1): The boy was born with a Wolff-Parkinson-White syndrome and had his first tachycardia with a heart rate of 295/min at the age of 20 days. After successful cardioversion with adenosine intravenously he received 4 mg/kg propranolol orally. After his 5th recurrent tachycardia we changed to 10.5 mg/kg propafenone. After the 6th tachycardia with the age of 13 months we stopped pharmacotherapy with the age of 18 months. While supplementing omega-3-fatty acids he has no tachycardia up to the age of 10 years. He is waiting on his catheter ablation.

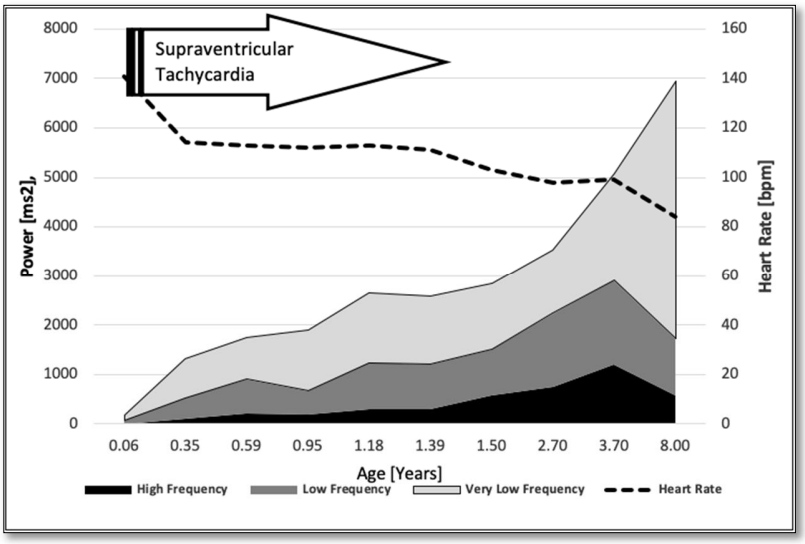


Figure 1. Case 1: Boy with Wolff-Parkinson-White syndrome.

Case 2 (Figure 2): The boy was born with a Mahaim-type accessory pathway with orthodrome and antidrome tachycardias. At his first presentation at the 14 day of life he has to be resuscitated due to a cardiogenic shock and a very high NT-Pro-BNP value of 94236 pg/ml. After successful cardiac recompensation with 4mg/kg propranolol he had further self-limiting tachycardias up to 280 bpm. After the

addition of 4 mg/kg amiodarone he was in a stable sinus rhythm and amiodarone was stopped at the 250 days of life.

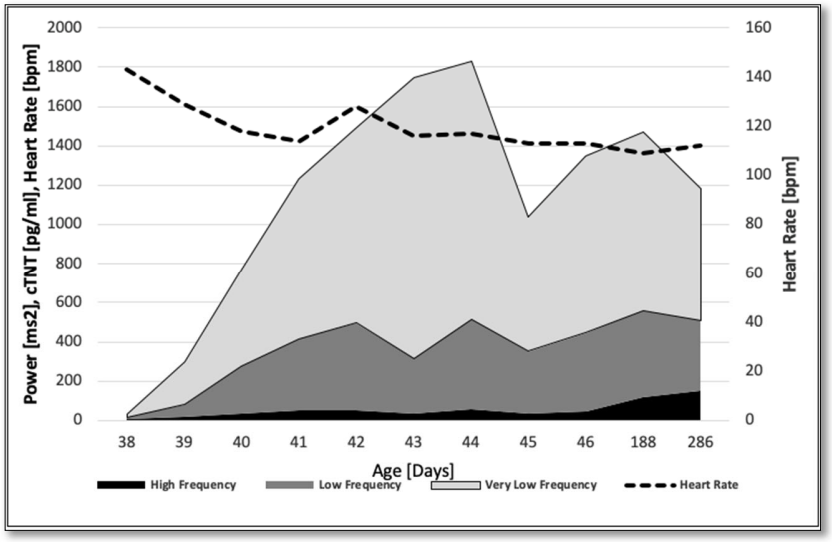


Figure 1. Case 2: Boy with Mahaim-type accessory pathway with orthodrome and antidrome tachycardias.

Case 3 (Figure 3): The girl was born with a Wolff-Parkinson-White syndrome and had her first tachycardia at the age of 9 month. Staying in Morocco, she was primary treated with amiodarone. We changed to 10 mg/kg propafenone, but she had a further heavy tachycardia with a heart rate of 230 bpm one month later. Despite intravenous administration of adenosine, propafenone and 15,8 mg/kg amiodarone only short interruptions of this tachycardia could be achieved. After a long persistent episode with recurrend tachycardias, only an esmolole infusion stopped the arrhythmia. At admission she was treated with 10mg/kg amiodarone and 1.5 mg/kg propranolol. However, 14 days later she had a further tachycardia, successfully treated with adenosine. The NT-Pro-BNP level was elevated to 8324 pg/ml during the second tachycardia at day 220 and nearly normal at 821 pg/ml during the third tachycardia at day 237 while treated with amiodarone and propranolol. She now receives 5mg/kg amiodarone and 3 mg/kg propranolol and has no further tachycardia at the age of 21 months.

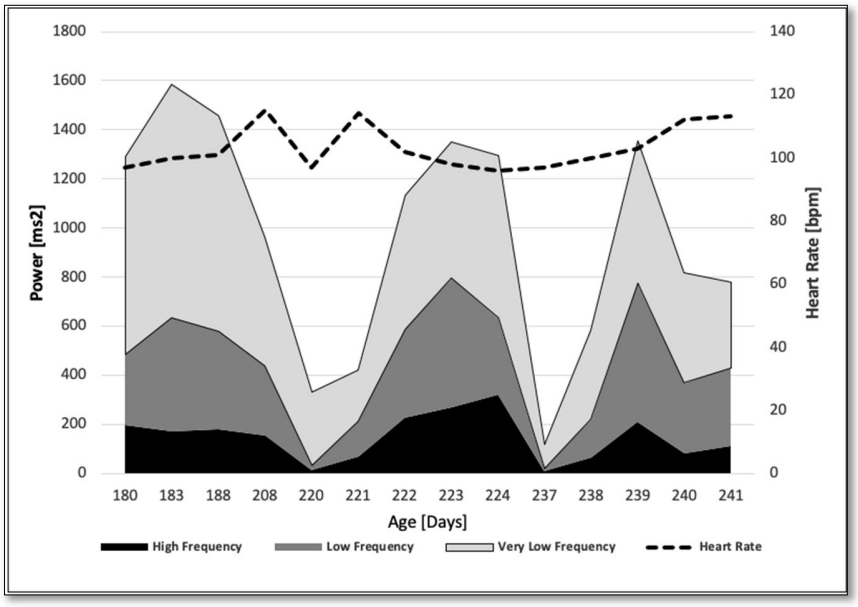


Figure 3. Case 3: Girl with Wolff-Parkinson-White syndrome.

Case 4 (Figure 4): The boy without a congenital heart defect had a sustained ventricular tachycardia in the 5th week of life. After adenosine and 1mg/kg propranolol, he received 5 mg amiodarone intravenously over 30 min. 20 min after the successful cardioversion, he developed a cardiogenic shock while having sinus rhythm and a heart rate of 95/min. Despite mechanical ventilation, he needed an escalation of the ongoing epinephrine therapy up to 1µg/kg/min due to pump failure of the left heart in echocardiography and a severe metabolic acidosis (pH: 7.04; BE: -20.2). The ECG shows deep ST depressions starting 37 min after cardioversion up to 43 min after cardioversion **(Figure 5)**. The Troponin T value was elevated with 150 pg/ml and increase to 363 pg/ml after cardioversion. The NT-Pro-BNP value was elevated with 30818 pg/ml. Despite a multiorgan failure with heart failure, renal failure, and liver failure the boy completely recovers within one week. With a low metoprolol therapy, he had no further ventricular tachycardia in his home monitoring.

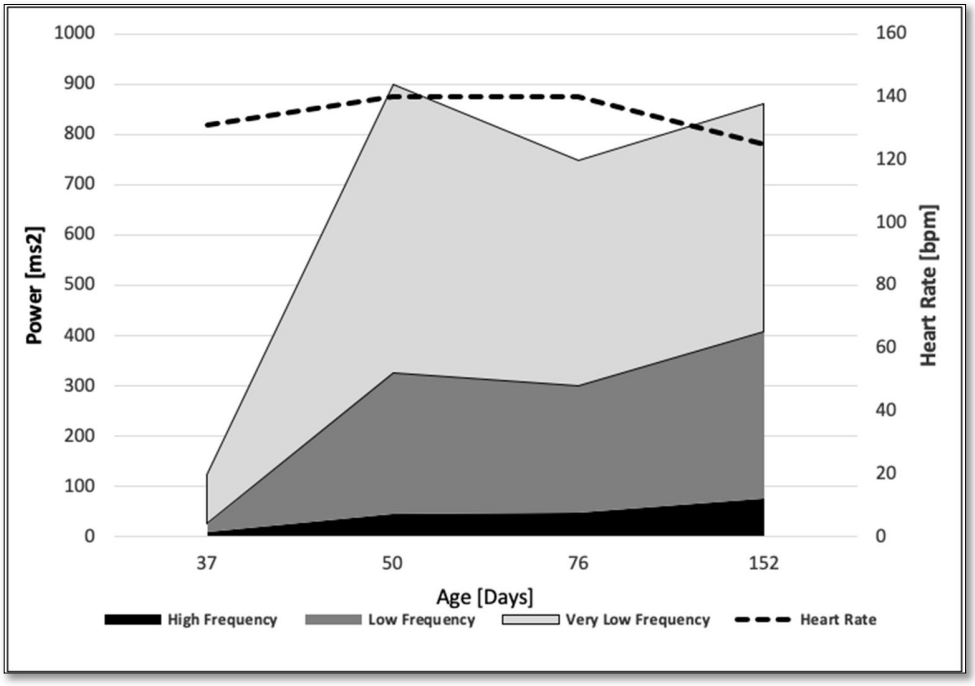


Figure 4. Case 4: Boy with a sustained ventricular tachycardia in the 5th week of life.

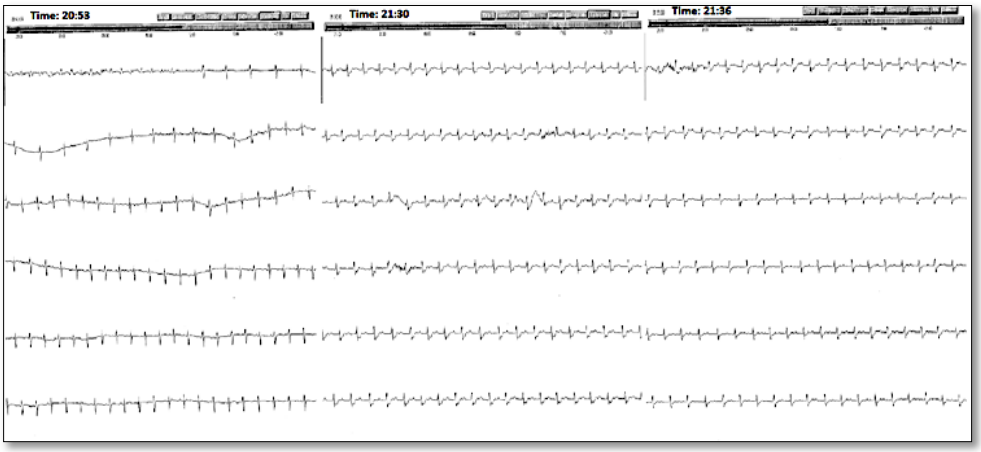


Figure 5. ECG of Case 4 showing deep ST depressions starting 37 min after cardioversion up to 43 min after cardioversion.

Case 5 (Figure 6): The boy was born with atrial fibrillation and a tachycardia with 215 bpm. The mother was treated by the obstetrics with digoxin and verapamil. Intravenous adenosine and 2 mg/kg propafenone were not successful. After 3 mg amiodarone within 20 min intravenously the boy converted to sinus rhythm with a heart rate of 140 bpm.

Immediately after cardioversion the ECG showed deep ST depressions over 5 min and the boy have to be resuscitated **(Figure 6)**. Despite immediate mechanical ventilation and a 0.2 µg/kg/min suprarenin perfusor he developed a cardiogenic shock with a pH: 6.97 and BE: -26.7. He completely recovers within 2 days and never had further atrial fibrillation or heart disease up to his current age of 9 years.

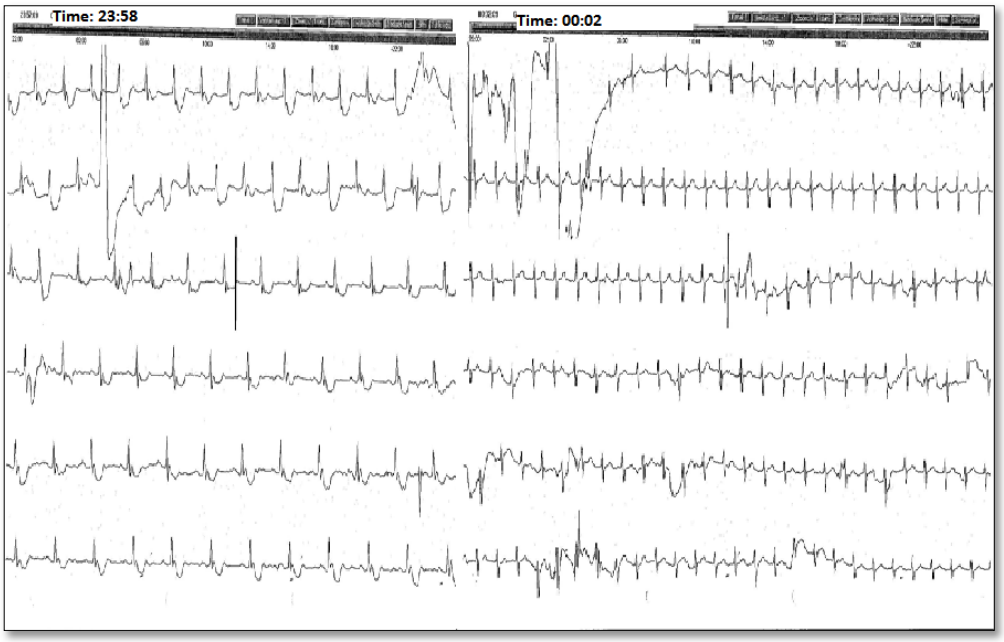


Figure 6. ECG of Case 5.

Case 6 (Figure 7): This girl was born with a hypoplastic right ventricle due to D-transposition of the great arteries with a severe hypoplasia of the aortic arch. She received a Damus-Kaye-Stansel operation at an age of one month and the total cavopulmonary connection at the age of two years. Non-sustained ventricular tachycardia was noticed for the first time in the course of the investigation of her fourth febrile seizure at the age of 6.5 years. The arrhythmia completely disappears during up-titration with propranolol at dosage of 3.5 mg/kg bodyweight.

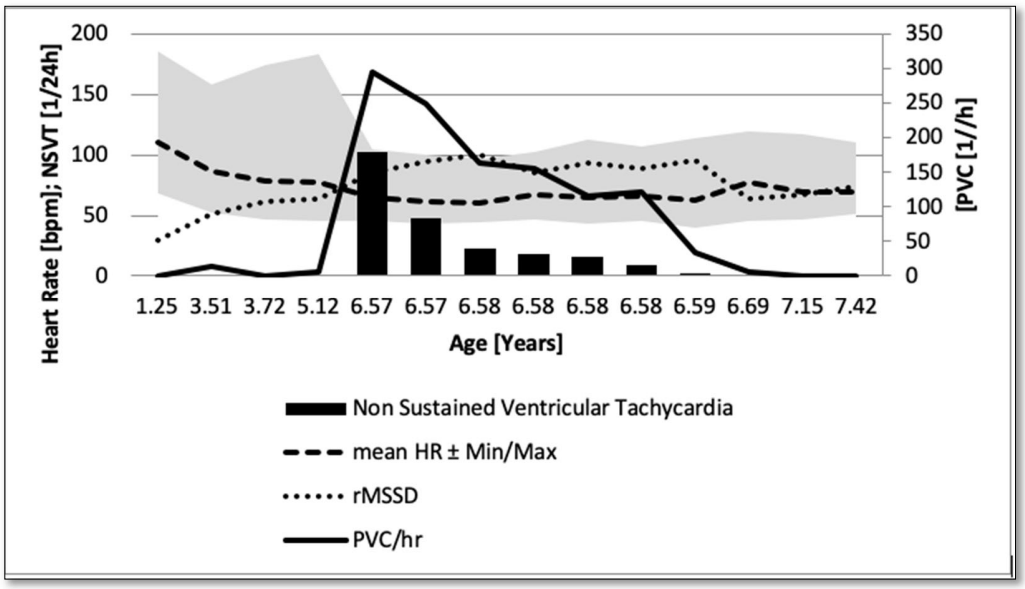


Figure 7. Case 6: Girl born with a hypoplastic right ventricle due to D-transposition of the great arteries with a severe hypoplasia of the aortic arch.

Case 7 (Figure 8): This boy was born with a Noonan syndrome and needed cardiac surgery of because of a severe pulmonary valve stenosis. He received metoprolol of to prevent arrhythmias due to his hypertrophic cardiomyopathy. However, non-sustained ventricular tachycardia was noticed for the first time at the age of 5.6 years. We change to propranolol and the arrhythmia completely disappears during up-titration with propranolol in two steps at a dosage of 6.0 mg/kg bodyweight.

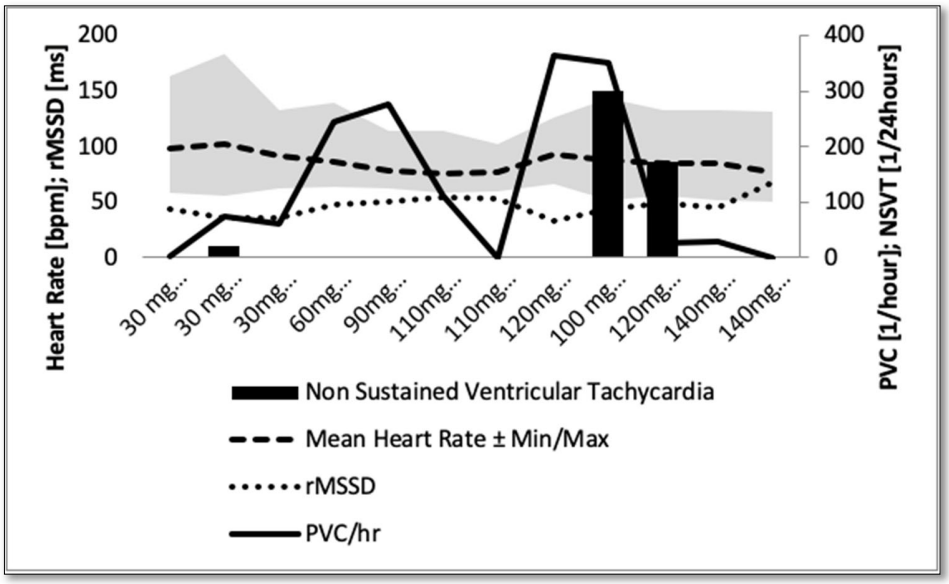


Figure 8. Case 7: Boy born with a Noonan syndrome.

Case 8 (Figure 9): Figure 9 demonstrates a spontaneous, unperceived, and untreated paroxysmal supraventricular tachycardia in a 16 years old boy at night while sleeping (3: 26 and 4: 11). HRV analysis demonstrates a phasic increase of total power in all frequencies immediately after the tachycardia and a very low total power during the tachycardia. The boy had successful catheter ablation and need no pharmacotherapy.

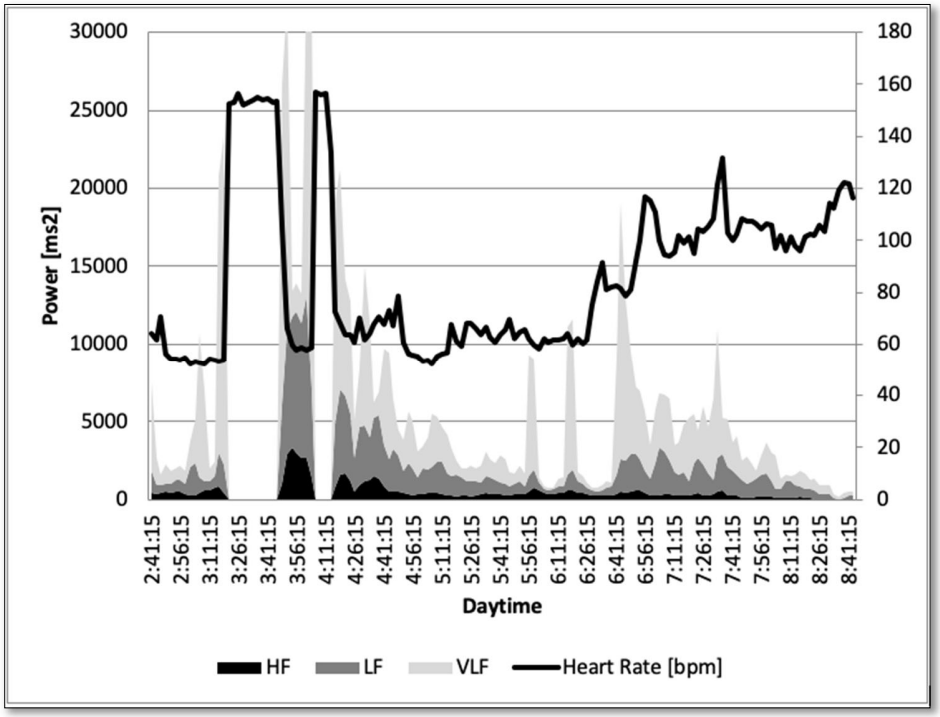


Figure 9. Case 8: Spontaneous, unperceived, and untreated paroxysmal supraventricular tachycardia.

Case 9 (Figure 10): This 15-year-old boy suffer from paroxysmal atrial fibrillation which was treated with the "pill in the pocket" (600 mg propafenone). Cardioversion to sinus rhythm was successful at 19: 22. An artificial high HRV during atrial fibrillation between 8:00 and 19:22 and a low HRV in the sinus rhythm could be detected.

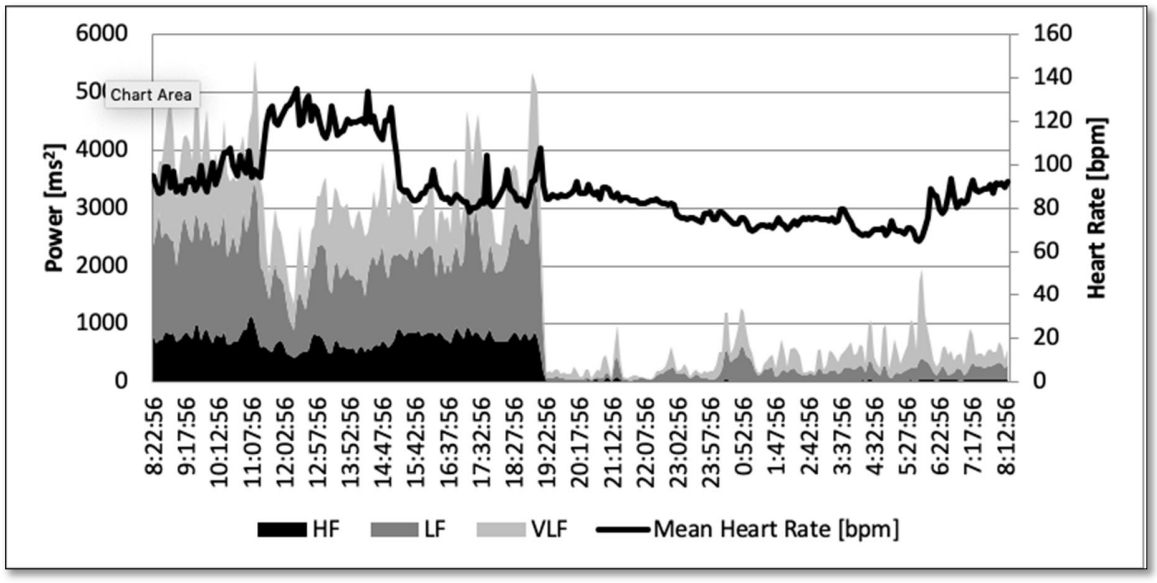


Figure 10. Case 9: 15-year-old boy suffer from paroxysmal atrial fibrillation.

Case 10 (Figure 11): This published case of a 15-year-old boy suffering from focal atrial tachycardia is recently published. After failure of catheter ablation and medical therapy, he received 2g omega 3 fatty supplementation while waiting on repeat ablation. Focal atrial tachycardia disappeared 4 weeks later, and antiarrhythmic therapy was terminated. We discuss the antiarrhythmic effect of omega 3 fatty acids on the autonomous nervous system based upon seven 24-hours Holter electrocardiographs, starting after diagnosis: During sinus rhythm alternating with focal atrial tachycardia after catheter ablation and metoprolol/flecainide at an age of 15.0 years the heart rate variability seems to be high. After resolution of focal atrial tachycardia with omega 3 fatty acid supplementation, the HRV decreased to low values that indicates autonomic dysfunction. The follow up to 2 years shows a slow recovery of heart rate variability.

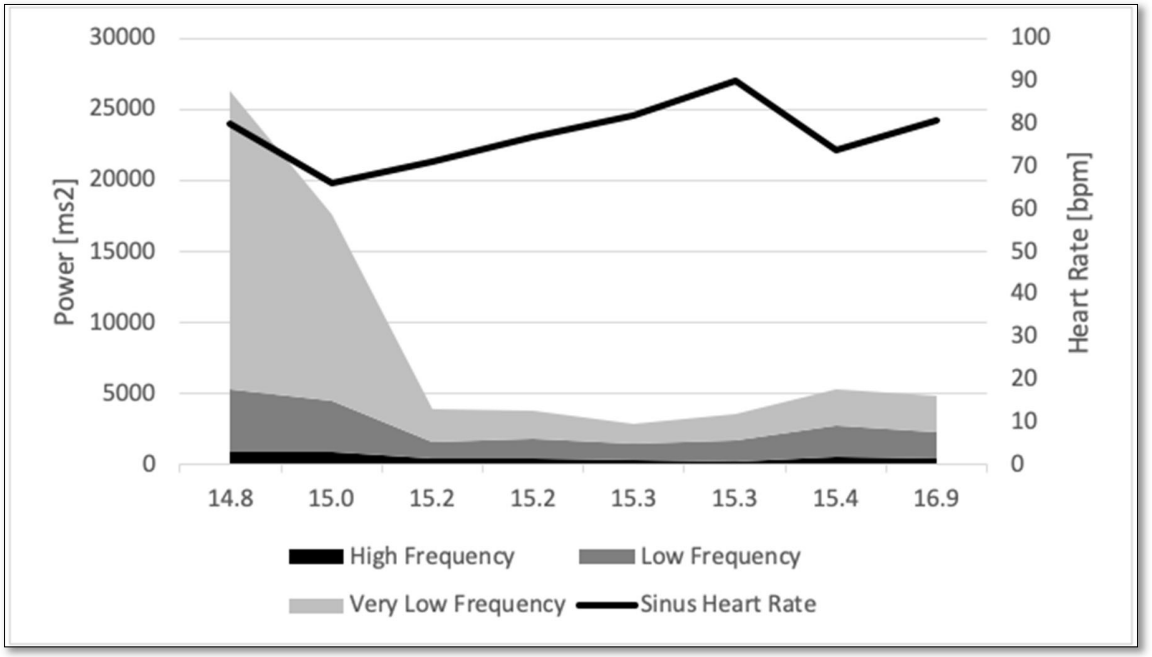


Figure 11. Case 10: A 15-year-old boy suffering from focal atrial tachycardia.

DISCUSSION

Pitfalls of assessment of autonomic function by heart rate variability in patients with arrhythmias

An essential prerequisite for an HRV analysis is a sinus rhythm with more than 90% analyzable QRS complexes. Arrhythmias and artifacts are more or less well excluded by the Holter ECG software and the editing of an experienced cardiologist. However, some arrhythmias are not detected by the software and the results are unreliable, as shown in case 8-10.

Case 8 shows the low HRV during a supraventricular tachycardia and the "autonomic storm" after this tachycardia. The tachycardia itself has to be excluded from HRV analysis.

Case 9 shows the artificial high HRV during atrial fibrillation that has to be excluded from HRV analysis.

Case 10 shows the artificial high HRV in a boy with focal atrial tachycardia that are excluded by the software. However, the short runs disturb the sinus rhythm and HRV analysis showed a very high Total Power. After resolution of focal atrial tachycardia with omega 3 fatty acid supplementation, the HRV decrease to low values that indicates the underlying autonomic dysfunction.

Heart Rate variability analysis and arrhythmias–clinical view

Infants with life threatening arrhythmias **(Cases 1-5)** have very low HRV immediately after the cardioversion to sinus rhythm. Probably it is a sign of heart failure indicated by very high NT-Pro-BNP levels (Case 2-4) [6]. This low global HRV indicated by low Total Power is comparable to infants' with severe heart failure with values below the 5th percentile **(Figure 12)**. In contrast to heart failure in congenital heart disease and cardiomyopathies, we start propranolol treatment with therapeutic doses between 1-4 mg/kg that was well tolerated in infants with a "healthy myocardium".

However, propranolol is a poor antiarrhythmic and for prophylactic drug therapy patients need propafenone or amiodarone in resistant cases **(Cases 1-4)**. The combination of amiodarone as an antiarrhythmic and propranolol to improve HRV is probably the most effective combination therapy **(Case 4)**.

For prophylactic therapy in infancy we should support the physiological maturation of the autonomic nervous system by supplementing omega-3-fatty acids. We have proofed the effect in different indications and found an increase of HRV and decrease of heart rates in nearly all children with reduced HRV [7]. The higher the increase of HRV, the earlier we can stop the antiarrhythmic prophylaxis. Further we report the resolution of a therapeutic resistant supraventricular tachycardia in 15 years old boy [8] by catheter ablation and double antiarrhythmic therapy by using omega-3-fatty acid supplementation **(Case 10)**.

Intravenous amiodarone is an effective treatment for a variety of ventricular and supraventricular arrhythmias in adults. Several studies have documented the effectiveness in the management of pediatric arrhythmias [9]. However, a recent publication reports a so-called amiodarone collapse in 47 of 456 children who received amiodarone. Among these children 45% need extracorporeal life support, 36% cardiopulmonary resuscitation, 13% inotropic support and 9 children died [10]. We report about two infants who have to be resuscitated after intravenous amiodarone **(Case 4 and 5)**. We try to understand this severe underreported complication using HRV-monitoring: The complication occured immediately after cardioversion **(Case 5)** or a few minutes later **(Case 4)** [11]. The ECG showed deep ST-Depression **(Figures 5 and 6)** and echocardiography severe pump failure of the left ventricle. The increase of Troponin T level (Case 4) indicated myocardial ischemia. We need high urgency mechanical ventilation and high epinephrine dosages to save the babies lives. Today, we propose electrical cardioversion in infants <3 month, who do not respond to adenosine of cause atrial fibrillation or ventricular tachycardia.

Sudden death prophylaxis in older children with congenital heart disease or Noonan cardiomyopathies is much more complicated. We use the concept of Ostmann-Smith et al. [11], who treat with very high propranolol dosages to limit the maximal heart rate. This effect is well documented in **Cases 6 and 7**. HRV analysis shows a slight improvement after propranolol, but we do not use HRV analysis to predict sudden cardiac death in individual patients and take care on the current guidelines.

However, we used HRV guided treatment in children with frequent premature ventricular captures that is not a life-threatening arrhythmia. These premature ventricular captures depend on HRV in children with a healthy heart but autonomic dysfunction due to obesity, attention deficit disorder or other psychosomatic disease **(Figure 13)** [12]. Omega-3-fatty supplementations reduces the number of premature ventricular captures by 50% on average and improve heart rate variability [7]. Other authors show the beneficial effect on cognition without any side effects [13].

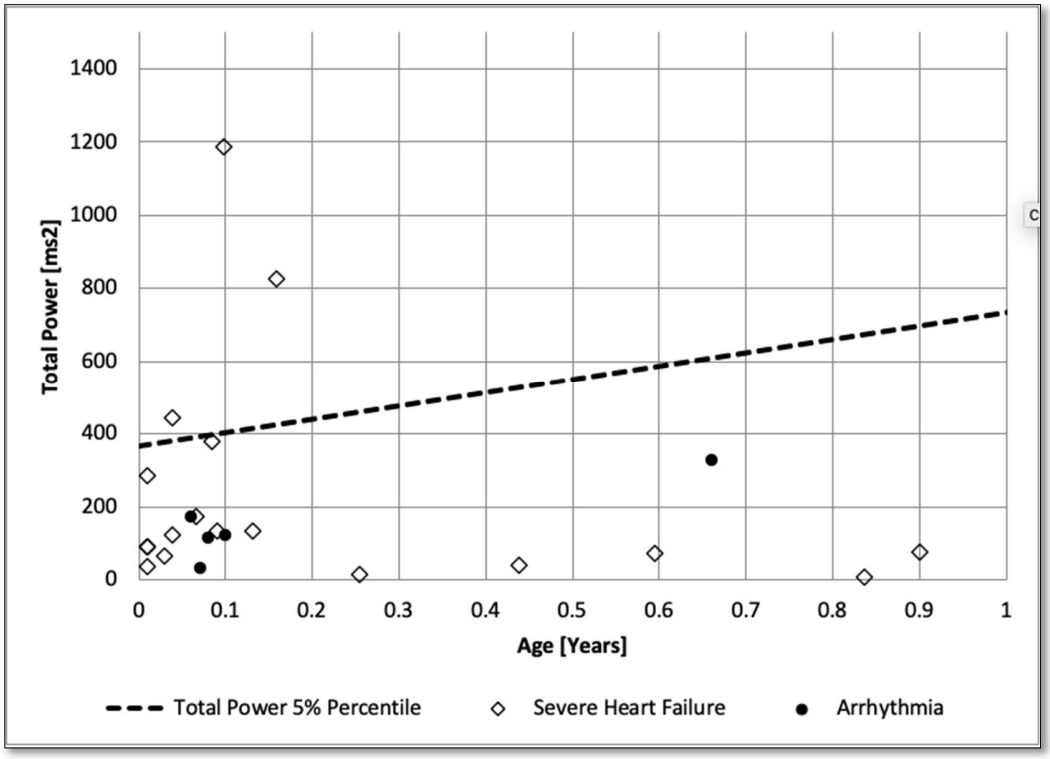


Figure 12. Age to total power plot showing the 5th percentile in infants. Patients with severe heart failure (open rhombus)(1) or life threatening arrhythmias (filled circle) are shown.

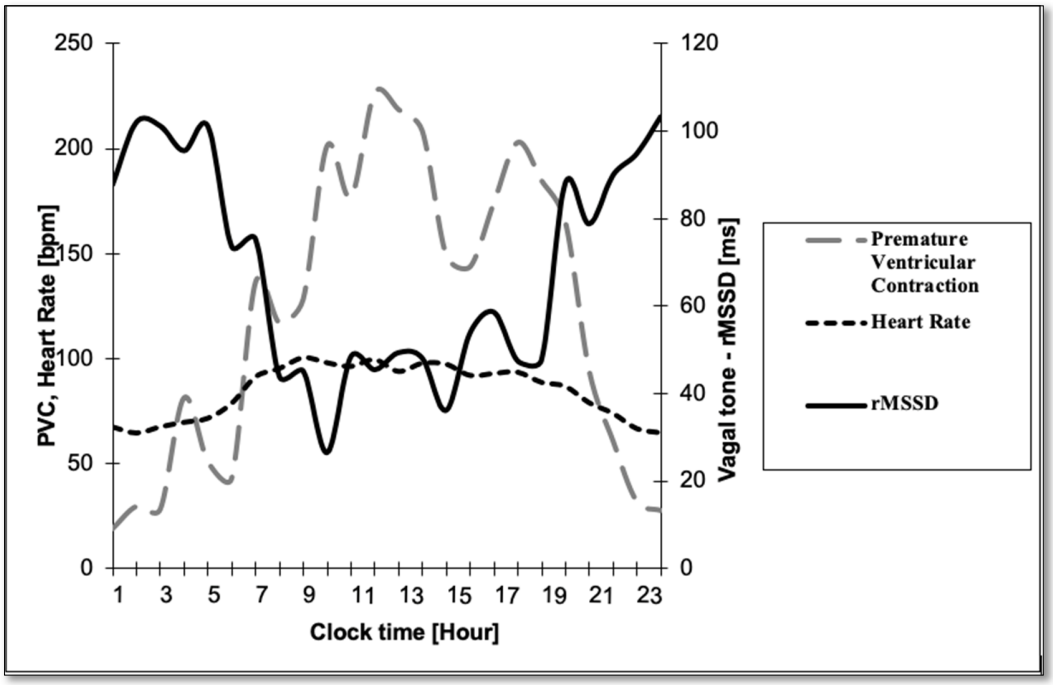
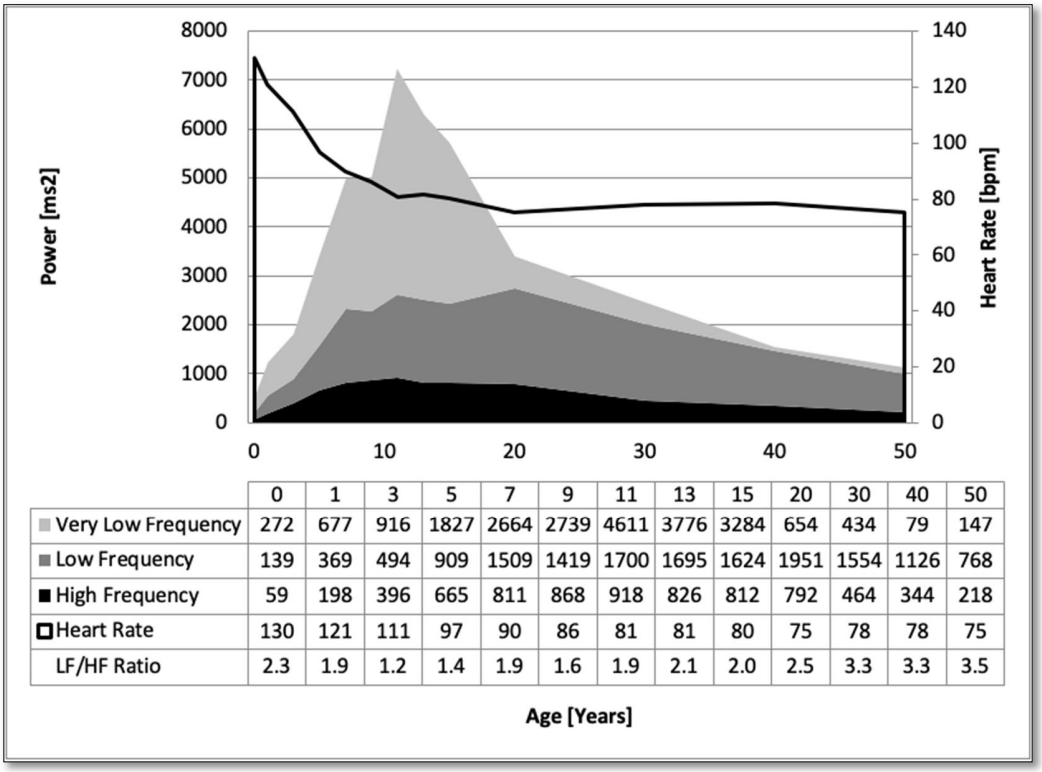


Figure 13. Mean hourly values of premature ventricular contractions, heart rate and the heart rate variability parameter rMSSD that represents vagal tone in 7 children with a significant circadian rhythm. Premature ventricular contractions significantly correlate with heart rate ($r=0.77$; $p<0.0001$) and rMSSD ($r=-0.83$; $p<0.0001$).



	0	1	3	5	7	9	11	13	15	20	30	40	50
Very Low Frequency	272	677	916	1827	2664	2739	4611	3776	3284	654	434	79	147
Low Frequency	139	369	494	909	1509	1419	1700	1695	1624	1951	1554	1126	768
High Frequency	59	198	396	665	811	868	918	826	812	792	464	344	218
Heart Rate	130	121	111	97	90	86	81	81	80	75	78	78	75
LF/HF Ratio	2.3	1.9	1.2	1.4	1.9	1.6	1.9	2.1	2.0	2.5	3.3	3.3	3.5

Figure 14. Heart rate and the power spectrum of healthy children and adults measured with the Fast Fourier (HRV) Analysis during the first 50 years of life including the reference data of Böckelmann et al. [14].

Figure 14 shows the heart rate and the power spectrum of healthy children and adults measured with the Fast Fourier (HRV) Analysis during the first 50 years of life including the reference data of Böckelmann et al. [14]. The high total power of school children mostly depends on the very low frequency power of the power spectrum with a peak at 11 years. The mean 24 h heart rate shows a decline up to the 11 years of life. The sympatho vagal balance indicated by the LF/HF ratio cannot explain the different heart rate in different age groups, that is probably regulated by the intrinsic heart rate.

The theoretical background of HRV analysis in patients with arrhythmias

Looking to the HRV during the first 50 years of the human life cycle **(Figure 14)**, humans have a very low global HRV indicated by the Total Power in the first year of life and later at the end of life [14]. There is a higher risk of sudden death during these periods with low HRV [15,16]. However, low HRV seems to be a more inevitable part of the human life cycle, but HRV can be modified by different cofounders, most all by nutrition and physical activity [17]. However, many diseases reduce global HRV with an impact on prognosis. The five children with life threatening arrhythmias **(Cases 1-5)** as well as the infants with severe heart failure [1] have similarly low Total powers as shown in **(Figure 12)** but most of them had a treatable disease. We are deeply convinced that each therapy with an impact prognosis–pharmacotherapy as well as surgery–must improve these low HRV. The current case collection and the recently published case collection of infants with severe heart failure demonstrate the advantage of an HRV guided pharmacotherapy that clearly demonstrate the improvement of HRV during a successful therapy.

There are contradicting hypothesis why prognosis was paralleled with the decline of HRV that have to be discussed [18]. In the first 20 years, we saw the changes in HRV as an expression of a change in the sympatho-vagal balance. Today we are convinced that HRV regulation takes place in at least three dimensions-the vagus, the sympathicus and the intrinsic heart rate most of all regulated by the HCN4 channels [19]. At the end of life heart rate was dominated from the intrinsic heart rate with little influence of the vagus and sympathicus. The tachogram of HRV (time versus heart rate) of case 4 immediately after his resuscitation of cause an amiodarone collapse **(Figure 15)** showed unusual pattern with heart rate fluctuations for 90 minutes after this severe complication. We anticipate this pattern as a decoupling and coupling of the autonomic nervous system on heart rate regulation only seen in dying or resuscitated children. The high-frequency vibrations in these tachograms presumably reflect the fundamental vibration of the sinus node cells if they are not under the control of the autonomous nervous system.

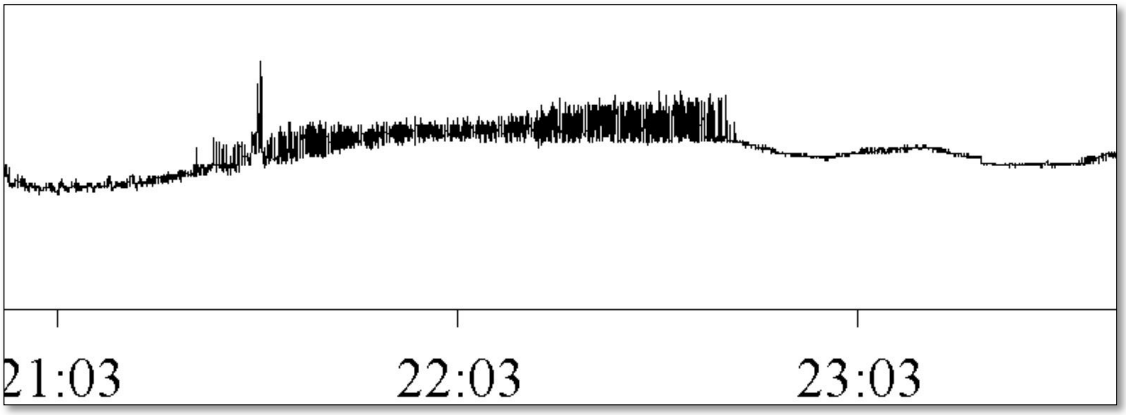


Figure 15. Case 4: Heart rate tachogram (time versus heart rate) of Case 4 who had Amiodarone collapse after cardioversion at 20:53 of a sustained ventricular tachycardia. He converted to sinus rhythm and a heart rate of 95/min. The tachogram show unusual fluctuations that suddenly stopped at 22:45 while clinical recovery.

DISCLOSURE

Authors have nothing to disclose and have no conflict of interest.

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