

The effect of antiretroviral therapy on the frequency and severity of cardiac arrhythmias in HIV-infected patients

V. M. Kovalenko*^{1,A,E,F}, V. A. Vasylenko^{2,A-D}, V. A. Potabashnij^{2,A,E,F}, A. M. Vasylenko^{2,E,F}

¹SI "National scientific center "M. D. Strazhesko Institute of Cardiology" NAMS of Ukraine, Kyiv, ²SI "Dnipropetrovsk Medical Academy Ministry of Health Ukraine", Kryvyi Rih

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*E-mail: support@example.com

The aim to study the effects of ART on the incidence and severity of supraventricular ectopy (SVE) and ventricular ectopy (VE) in HIV-infected patients.

Materials and methods. We analyzed the results of ambulatory monitoring ECG (AM ECG) in 43 HIV-infected patients before and after antiretroviral therapy (ART). The amount of serum high sensitivity C-reactive protein (hsCRP) was determined in all patients.

Results. In all patients before prescribing ART and one year after ART, SVE was registered with varying severity, whereas VE was registered in 28 (93.3 %) patients of the control group. VE was detected in 31 (72.1 %) patients before prescribing ART, 27 (62.5 %) patients after a year of receiving ART and 6 (20 %) patients in the control group.

After analyzing the structure of SVE and VE, it was noted that in HIV-infected patients before ART, a greater number of SVE and VE was recorded, which were significantly decreased when the virological and immunological goals of ART were achieved. Patients showed an increase in the SDNN index to 148.3 ± 11.2 ms and SDANN to 133.3 ± 8.3 ms after effective ART.

There were not significant changes in other time-domain heart rhythm variability (HRV) indicators (SDNN, SDNN-index, pNN50 and rMSSD) in this group. A decrease in the frequency and severity of SVE and VE as well as HRV profile improvement were registered with a decrease in the concentration of highly sensitive CRP from 19.1 ± 2.2 mg/l to 10.7 ± 1.3 mg/l ($P < 0.05$).

Conclusions. In HIV-infected patients, both supraventricular and ventricular ectopy are more pronounced and significantly more frequently recorded, including ectopic rhythms which are not peculiar to healthy people. In HIV-infected patients on antiretroviral therapy for 52 ± 4 weeks when viral load <20 copies/ml and CD4+ T lymphocytes >400 cells/ml are reached, the frequency of supraventricular and ventricular ectopy registration is significantly decreased.

In HIV-infected patients, a decrease in supraventricular ectopy and ventricular ectopy intensity occurs coupled with a decrease in the level of hsCRP, as well as an improvement in the integral time and spectral indices of heart rate variability. This suggests that systemic inflammatory response and hypersympathicotonia are pathogenetic links of arrhythmogenesis in HIV-infected patients.

Ключові слова:

ВІЛ-інфекція, антиретровірусна терапія, амбулаторне монітування ЕКГ, екстрасистола передсердна, варіабельність серцевого ритму, С-реактивний протеїн.

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Вплив антиретровірусної терапії на частоту та вираженість надшлуночкових і шлуночкових порушень ритму серця у ВІЛ-інфікованих пацієнтів

В. М. Коваленко, В. А. Василенко, В. А. Потабашній, А. М. Василенко

Мета роботи – вивчити вплив антиретровірусної терапії (АРТ) на частоту й вираженість суправентрикулярної (СВЕ) і шлуночкової ектопії (ШЕ) у ВІЛ-інфікованих пацієнтів.

Матеріали та методи. Проаналізували результати амбулаторного монітування ЕКГ (АМ ЕКГ) у 43 ВІЛ-інфікованих пацієнтів до та після призначення АРТ. У всіх пацієнтів визначили рівень високочутливого С-реактивного протеїну (вСРП) сироватки крові.

Результати. У всіх пацієнтів до призначення АРТ і через рік приймання АРТ зареєстрована СВЕ різного ступеня вираженості, тоді як у контрольній групі СВЕ – у 28 осіб (93,3 %). Шлуночкову ектопію виявили у 31 (72,1 %) пацієнта до приймання АРТ, 27 (62,5 %) пацієнтів – після приймання і в 6 (20 %) осіб контрольної групи.

Проаналізувавши структуру СВЕ та ШЕ, відзначили, що у ВІЛ-інфікованих пацієнтів до АРТ реєструється більше і СВЕ, і ШЕ, котрі істотно зменшуються при досягненні вірусологічних та імунологічних цілей АРТ. На тлі ефективної АРТ у пацієнтів після АРТ відзначено збільшення показника SDNN до $148,3 \pm 11,2$ мсек і SDANN – до $133,3 \pm 8,3$ мсек. Істотної зміни інших часових показників варіабельності серцевого ритму (BCP) (SDNN-index, pNN50 і rMSSD) у цій групі не виявили. Зменшення частоти та вираженості СВЕ та ШЕ, а також поліпшення профілю BCP зареєстровані на тлі зниження концентрації вСРП із $19,1 \pm 2,2$ мг/л до $10,7 \pm 1,3$ мг/л ($p < 0,05$).

Висновки. У ВІЛ-інфікованих пацієнтів вірогідно частіше реєструється та значно виражена суправентрикулярна та шлуночкова ектопія, зокрема й ектопічні ритми, нехарактерні для здорових. У ВІЛ-інфікованих пацієнтів на тлі АРТ протягом 52 ± 4 тижнів при досягненні вірусного навантаження <20 копій/мл і CD4+ Т-лімфоцити >400 кл/мл частота реєстрації кількості суправентрикулярних і шлуночкових ектопій вірогідно знижується.

У ВІЛ-інфікованих пацієнтів зменшення вираженості СВЕ та ШЕ відбувається на тлі зниження рівня вСРП, а також поліпшення інтегральних часових і спектральних показників варіабельності серцевого ритму. Це дає підстави вважати, що системна запальна відповідь і гіперсимпатикотонія є патогенетичними ланками аритмогенезу у ВІЛ-інфікованих пацієнтів.

Влияние антиретровирусной терапии на частоту и выраженность нарушений ритма сердца у ВИЧ-инфицированных пациентов

В. Н. Коваленко, В. А. Василенко, В. А. Потабашний, А. М. Василенко

Цель работы – изучить влияние антиретровирусной терапии (АРТ) на частоту и выраженность суправентрикулярной (СВЭ) и желудочковой эктопии (ЖЭ) у ВИЧ-инфицированных пациентов.

Материалы и методы. Проанализировали результаты амбулаторного мониторинга ЭКГ (АМ ЭКГ) у 43 ВИЧ-инфицированных пациентов до и после назначения АРТ. У всех пациентов определяли уровень высокочувствительного С-реактивного протеина (вЧСРП) сыворотки крови.

Результаты. У всех пациентов до назначения АРТ и через год приема АРТ зарегистрирована СВЭ разной степени выраженности, тогда как в контрольной группе СВЭ зарегистрирована у 28 человек (93,3 %). ЖЭ установлена у 31 (72,1 %) пациентов до АРТ, 27 (62,5 %) пациентов после АРТ и 6 (20 %) человек контрольной группы. Проанализировав структуру СВЭ и ЖЭ, отмечено, что у ВИЧ-инфицированных пациентов до АРТ регистрируется большее количество как СВЭ, так и ЖЭ, которые существенно уменьшаются при достижении вирусологической и иммунологической целей АРТ.

На фоне эффективной АРТ у пациентов после приема зафиксировано увеличение показателя SDNN до $148,3 \pm 11,2$ мсек и SDANN до $133,3 \pm 8,3$ мсек. Существенного изменения других временных показателей вариабельности сердечного ритма (BCP) (SDNN-index, pNN50 и rMSSD) в этой группе не отмечено. Уменьшение частоты и выраженности СВЭ и ЖЭ, а также улучшение профиля BCP зарегистрированы на фоне снижения концентрации вЧСРП с $19,1 \pm 2,2$ мг/л до $10,7 \pm 1,3$ мг/л ($p < 0,05$).

Выводы. У ВИЧ-инфицированных пациентов достоверно чаще регистрируется и более выражена суправентрикулярная и желудочковая эктопия, в том числе эктопические ритмы, не характерные для здоровых. У ВИЧ-инфицированных пациентов на фоне АРТ в течение 52 ± 4 недели при достижении вирусной нагрузки <20 копий/мл и CD4+ Т-лимфоциты >400 кл/мл частота регистрации количества СВЭ и ЖЭ достоверно снижается. У ВИЧ-инфицированных пациентов уменьшение выраженности СВЭ и ЖЭ происходит на фоне снижения уровня вЧСРП, а также улучшения интегральных временных и спектральных показателей вариабельности сердечного ритма. Это дает основания считать, что системный воспалительный ответ и гиперсимпатикотония являются патогенетическими звеньями аритмогенеза у ВИЧ-инфицированных пациентов.

Ключевые слова: ВИЧ-инфекция, антиретровирусная терапия, амбулаторное мониторирование ЭКГ, экстрасистола предсердная, вариабельность сердечного ритма, С-реактивный протеин.

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HIV-infected patients have a higher risk of developing cardiovascular disease [7,10]. In comparison with the general population, these patients in 4.5 times more often to have sudden cardiac death caused by anamnesis of myocardial infarction, cardiomyopathy, heart failure, and ventricular arrhythmias [11,12]. Cardiovascular abnormalities are common in HIV-infected individuals but often go unrecognized or untreated which results in increased cardiovascular-related morbidity and mortality and reduced quality of life. Clinicians may mistakenly attribute signs of cardiovascular abnormalities to pulmonary or infectious causes, an error that can delay appropriate treatment [9]. Despite the fact that the majority of HIV-infected patients die from AIDS-related diseases, sudden arrhythmic death is a significant risk factor for mortality in HIV-infected patients [2,8,11,12].

Electrocardiographic abnormalities are more commonly found in HIV-infected patients compared with HIV-negative patients. Disturbances of intraventricular conduction, isolated changes of the ST segment and T wave as well as QT interval prolongation were found in 8 % of HIV-positive patients resulting in a 2-fold increase in cardiovascular events in this category of patients. In most cases, ECG changes were reversible during antiretroviral therapy (ART). This may indicate that due to the high viral load (VL) and low CD4+ T lymphocytes count, these patients had ECG signs of myocarditis (HIV-associated) a frequency of which decreased in the context of ART [6].

The incidence of atrial fibrillation (AF) in HIV-infected individuals is 3.6 cases per 1000 person-years (95 % CI: 3.4–3.9) [3]. In 780 (2.6 %) of the 30,000 HIV-infected patients observed, permanent AF developed within 15 years of follow-up. Often, in HIV-infected individuals, a decrease in CD 4+ and an increase in VL are independent risk factors for AF

development. A possible pathogenetic mechanism linking AF and HIV infection is systemic inflammation [5].

Currently, there are few reports in the literature about the effect of ART on the frequency and severity of cardiac arrhythmias in HIV – infected patients, which formed the basis for our study.

Purpose of the study

To study the effects of ART on the incidence and severity of supraventricular ectopy (SVE) and ventricular ectopy (VE) in HIV-infected patients.

Materials and methods

The work was performed in RCI “Kryvyi Rih Center for Prevention and Control of AIDS” during the period from 2016 to 2018. We analyzed the results of ambulatory ECG monitoring (AM ECG) in 43 HIV-infected patients registered in this medical institution before and after initiation of ART who achieved an undetectable level of VL (less than 20 copies/ml) and the immunological goal of increasing CD4 count >400 cells/ml. Heart rate variability (HRV) indices and serum levels of high-sensitivity C-reactive protein (hsCRP) were evaluated in all the examined patients.

CD4+ T-lymphocytes count was determined by flow cytometry using an automated biochemical analyzer Random Access A-15, BioSystems S.A.

Plasma concentration of hsCRP was measured by a latex particle enhanced immunoturbidimetric assay on a Roche Cobas c311 chemistry analyzer (Roche Diagnostics) which allows determining hsCRP level in the range of 1.00–250 mg/l.

The AM ECG was performed using the DX-AKM-03 ArNika hardware and software complex (Kharkiv). HRV was analyzed by the following time-domain indicators: the standard deviation of total normal R-R intervals during the 24-hour period (SDNN, ms); the mean of the standard deviations of all normal R-R intervals for all 5-min segments during the 24-hour period (SDNN index, ms); root mean square differences of the standard deviation during the 24-hour period (rMSSD, ms); percentage of beats that changed more than 50 ms from the previous beat (pNN50, %). The spectral indices of HRV were also analyzed: high-frequency component (HF, %), low frequency component (LF, %) and the low frequency to high frequency component ratio (LF/HF). These indicators were chosen based on their informativity reflecting the influence of both sympathetic and parasympathetic nervous system on HRV [9].

Patients were compared before and after receiving ART:

– 43 HIV + patients before ART initiation.

– 43 HIV + patients received ART during 1 year (52 ± 4 weeks): 32 people (74.4 %) nevirapine (NVP)/zidovudine (AZT)/lamivudine (3TC), 11 people (25.6 %) – nelfinavir (NFV)/zidovudine (AZT)/lamivudine (3TC) and achieved CD4+ count more than 400 cells per ml and VL <20 copies/ml.

The re-examination interval was caused by the fact that longer ART in HIV-infected patients increases significantly the risk of developing coronary heart disease (CHD). In such patients, cardiac arrhythmias can be a manifestation of CHD and its complications [1,4,7].

– the control group consisted of 30 practically healthy individuals, matched by sex, age, body mass index. HIV-negative status of these people was confirmed by a screening test for detecting HIV antibodies produced by Beijing Wantai Biological Pharmacy Enterprise Co., Ltd, cat. No. WJ-1810E.

The inclusion criteria were: age ≥30 years, palpitations, stage I-III of HIV, VL < 100000 copies/ml; CD4+ T-lymphocytes count <400 cells/ml.

The exclusion criteria were: CD4+ T-lymphocytes count <200 cells/ml, VL >100,000 copies/ml; patients with drug addiction and alcoholism, acute inflammatory process, active tuberculosis and viral hepatitis B, C, thyroid gland pathology.

Clinical and demographic characteristics of the examined patients are presented in *Table 1*.

For statistical analysis of quantitative trait differences, a parametric Student's t-test for signs with a normal distribution pattern and Mann-Whitney non-parametric test for signs that differ from the normal distribution pattern, checking equality of group variances using Fisher's exact (one-sided) test in four-field tables were used. Statistical and mathematical data processing was performed using the licensed office suite Microsoft Excel and the application package Statistica (version 6.1), with the serial number AGAR909E415822FA (StatSoft Inc., USA). Data were presented as $M \pm m$, where M was the average value of the indicator, m was the standard error. Statistically significant differences were determined at $P < 0.05$.

Results

In AM ECG, the average heart rate (HR) during the day in patients before ART 95.3 ± 2.2 beats/min, after ART – 89.1 ± 2.4

beats/min ($P < 0.05$). In the control group, this indicator was 77.5 ± 0.4 beats/min. The average HR at night in patients before ART was 61.3 ± 1.4 beats/min, and in patients after ART – 61.4 ± 1.7 beats/min. In the control group, this indicator was 55.2 ± 0.2 beats/min.

Patients before ART, a significantly higher circadian heart rate index (CI) was registered, which was 155.4 ± 5.1 %, compared with patients after ART – 148.6 ± 5.5 % ($P < 0.05$). In the control group, CI was 143.8 ± 1.3 %. So, in HIV-infected patients who did not receive ART, an increase in the sympathetic influence of the autonomic nervous system was observed, which was manifested by higher values of the average HR during day and night periods, also a higher value of CI, compared with HIV-infected patients who achieved virological and immunological goals of ART.

At the same time, the patients after ART maintained significantly higher values of daytime and nighttime average HR compared with the control group, and the CI was not significantly different.

In all patients before and after ART, SVE was registered with varying degrees of severity, whereas SVE was registered in 28 (93.3 %) of patients in the control group.

Analyzing the structure of SVE, it was found that the number of isolated SVE was the maximum before ART accounting for 1846.3 ± 128.6 , which was significantly higher than in patients after ART – 1321.4 ± 142.1 ($P < 0.05$). The smallest number of isolated SVE (328.7 ± 19.4 , $P < 0.05$) was registered in the control group patients compared with both groups of HIV-infected patients.

SV allorhythmia (bi-, trigemina) was observed in 35 patients (81.4 %) before ART and in 32 (74.4 %) patients after ART. In the control group, SV allorhythmia was registered in 19 people (63.3 %). The total duration of SV allorhythmia in patients before ART was 26.3 ± 2.8 minutes, which was not significantly different from the patients after ART – 21.5 ± 3.1 minutes ($P > 0.05$). In the control group patients, this indicator was 4.2 ± 0.4 minutes that was significantly less compared with both groups of HIV-infected patients.

SVE couplets were registered in 25 (58.1 %) patients before ART, and in 13 (30.2 %) patients after ART. In the control group, SVE couplets were registered in 4 (13.3 %) people. SV triplets were recorded in 11 (25.6 %) patients before ART, 8 (18.6 %) patients after ART and in 2 people (6.7 %) in the control group. Herewith, the largest number of SV couplets and SV triplets were recorded in patients before ART (82.6 ± 7.4 and 41.1 ± 3.3 , respectively), which was significantly different from the indicators in patients after ART (59.4 ± 2.3 and 31.9 ± 1.1 ; $P < 0.05$, respectively) and the control group (14.8 ± 0.6 and 9.7 ± 0.3 , respectively).

In 9 (20.9 %) patients before ART, 9.7 ± 0.6 episodes of unstable supraventricular tachycardia (SVT) were recorded (up to 30 sec.). After ART – 7.3 ± 0.3 episodes of unstable SVT were reported in 5 (11.6 %) patients.

SVT events, which are not typical for healthy people, were registered in 2 patients before ART (4.65 %), and in 2 (4.6 %) patients after ART. The total duration of SVT events was significantly longer in patients before ART and lasted for 21.4 ± 3.8 minutes, compared with 11.4 ± 2.6 minutes ($P < 0.05$) in patients after ART. In the control group, episodes of unstable SVT and paroxysms of SVT were not recorded.

VE was detected in 31 (72.1 %) versus 27 (62.5 %) patients before and after ART, respectively, and in 6 (20 %) controls. Polymorphic VE was registered in 2 (4.65 %) patients before ART and it was not observed in other individuals.

The number of isolated VE was 986.2 ± 72.3 in patients before ART, whereas a significantly smaller its number was registered in patients after ART – 783.9 ± 59.4 ($P < 0.05$). In the control group, the number of isolated VE was significantly lower compared with the groups before and after ART, representing 108.4 ± 14.1 ($P < 0.05$).

Ventricular allorhythmia was registered in 18 patients (41.9 %) before ART with a total duration of 19.8 ± 3.6 minutes. After ART, ventricular allorhythmia was registered in 16 (37.2 %) patients and its total duration did not significantly differ from that in patients before ART (14.7 ± 2.7 ; $P < 0.05$). In the control group, the lowest indices of allorhythmia frequency and duration were observed (6.1 % and 2.1 ± 0.4 min, respectively). In both groups of HIV-infected patients, VE couplets and triplets were registered, but not being characteristics of healthy people, accordingly, these arrhythmias were not registered in the control group. Before ART, VE couplets were recorded in 13 patients (30.2 %) and their number was 56.1 ± 2.3 . After ART, VE couplets were recorded in 9 patients (20.9 %) and their number was significantly lower (44.7 ± 1.2 ; $P < 0.05$). A similar situation was observed when comparing the frequency of registration and number of VE triplets in HIV – infected patients: 4 (9.3 %) patients before ART versus 3 (6.9 %) patients after ART; 20.5 ± 1.8 versus 12.4 ± 0.8 , respectively ($P < 0.05$).

Therefore, in HIV-infected patients before ART initiation, a higher frequency and severity of both SVE and VE were recorded, which were significantly decreased after virological and immunological goals of ART achieving, but not reaching the values of practically healthy individuals.

After analyzing HRV in the examined patients, it was found to be decreased in patients before ART. It was manifested by a significant decrease in SDNN and SDANN, which are integral indicators characterizing the sympathetic and parasympathetic influences of the autonomic nervous system (ANS) on HRV, compared with the control group (SDNN, ms: 125.1 ± 8.4 vs. 169.1 ± 4.3 ($P < 0.05$); SDANN, msec: 114.3 ± 7.6 vs. 142.3 ± 3.6 ($P < 0.05$), respectively). At the same time, the SDNN-index in these groups did not significantly differ (40.2 ± 2.3 vs. 43.7 ± 0.9 ($P > 0.05$)). Time-domain indicators, reflecting the parasympathetic ANS influence, did not significantly differ between patients before ART and the control group (pNN50, %: 29.2 ± 4.3 vs. 34.9 ± 0.4 ($P > 0.05$) and rMSSD, ms : 32.6 ± 5.6 vs. 38.1 ± 0.6 , respectively) ($P > 0.05$).

Analyzing the spectral indices of HRV, we also noted the sympathetic effect predominance on HRV, which was manifested by a significant increase in the low-frequency component and the LF/HF ratio in patients before ART and the control group (LF, %: 68.2 ± 4.3 vs. 54.4 ± 0.3 ($P < 0.05$); LF / HF, units.: 2.31 ± 0.07 vs. 1.81 ± 0.04 ($P < 0.05$), respectively). Along with that, the high-frequency component did not significantly differ in the same groups (HF, %: 27.7 ± 3.1 vs. 28.6 ± 1.1 ($P > 0.05$)). The data above indicate an increase in the sympathetic effect of the ANS on HRV in HIV-infected patients who did not receive ART.

Table 1. Clinical and demographic characteristics of the examined patients

Indicators, units	Before ART (n = 43)	After ART (n = 43)	Control group (n = 30)
Average age, years	42.3 ± 2.8	43.1 ± 2.1	42.6 ± 1.9
Men, persons (%)	24 (47.6)	19 (44.2)	16 (53.3)
Women, persons (%)	27 (52.4)	24 (55.8)	14 (46.7)
BMI, kg/m ²	19.5 ± 2.4	21.7 ± 1.8	23.1 ± 1.2
SBP, mm Hg	124.3 ± 3.1	128.5 ± 2.9	125.8 ± 2.2
DBP, mm Hg	61.2 ± 2.5	64.3 ± 1.8	62.5 ± 1.3
CD4+ T-lymph, cells/ml	$264.2 \pm 13.4^*$	$497.3 \pm 36.7^{**}$	692.1 ± 74.4
VL, copies/ml	$74264 \pm 4216^*$	$<20^{**}$	N/A
hsCRP, mg/ml	$19.1 \pm 2.2^*$	$10.7 \pm 1.3^{**}$	4.1 ± 0.8

*: the difference is significant compared with the control group ($P < 0.05$);

#: the difference is significant compared to before ART ($P < 0.05$).

Table 2. Heart rate variability indicators in the examined patients

Indicators, units	Before ART (n = 43)	After ART (n = 43)	Control group (n = 30)
SDNN, ms	$125.1 \pm 8.4^*$	$148.3 \pm 11.2^{**}$	169.1 ± 4.3
SDANN, ms	$114.3 \pm 7.6^*$	$133.3 \pm 8.3^{\#}$	142.3 ± 3.6
pNN50, %	29.2 ± 4.3	34.1 ± 3.3	34.9 ± 0.4
SDNN index, msec	40.2 ± 2.3	44.7 ± 1.9	43.7 ± 0.9
rMSSD, ms	32.6 ± 5.6	36.6 ± 4.7	38.1 ± 0.6
LF, %	$68.2 \pm 4.3^*$	$53.3 \pm 1.1^{\#}$	54.4 ± 0.3
HF, %	27.7 ± 3.1	29.2 ± 2.6	28.6 ± 1.1
LF/HF, units	$2.31 \pm 0.07^*$	$1.84 \pm 0.08^{\#}$	1.81 ± 0.04

*: the difference is significant compared with the control group ($P < 0.05$);

#: the difference is significant compared to before ART ($P < 0.05$).

An improvement in HRV was noted in patients after achieving the virological and immunological ART goals. It was manifested by an increase in SDNN to 148.3 ± 11.2 msec and SDANN to 133.3 ± 8.3 msec. There were not significant changes in other time-domain HRV indicators (SDNN-index, pNN50 and rMSSD) in this group.

Improved spectral indices of HRV in patients after ART compared with those before ART were noted manifesting by a significant decrease in the LF/HF index and low-frequency component proportion, which did not differ from those in the control group (LF/HF: 1.84 ± 0.08 vs. 1.81 ± 0.04 ; LF: 53.3 ± 1.1 % vs. 54.4 ± 0.3 %, respectively). The high-frequency component percentage was not significantly different between the groups.

The identified changes indicate a decrease in sympathetic effects on the heart and an improvement in the HRV profile due to benefit of both integral time-domain parameters and spectral indices of HRV in HIV-infected patients while receiving ART.

In the course of an effective ART, HIV-infected patients showed a significant decrease in systemic inflammatory response severity, which was confirmed by a decrease in the concentration of hsCRP from 19.1 ± 2.2 mg/l to 10.7 ± 1.3 mg/l ($P < 0.05$). However, the concentration of hsCRP in HIV-infected patients, who achieved virological and immunological ART goals, remained significantly higher compared with that in the control group.

The dynamics of heart rate variability in HIV-infected patients in the course of 1-year ART is presented in Table 2.

The dynamics of SV and VE in HIV-infected patients in the course of 1-year ART is presented in Table 3.

Table 3. Frequency of SV and VE in the examined patients

Indicators		Before ART (n = 43)		After ART (n = 43)		Control group (n = 30)	
		n	%	n	%	n	
SVE (registration frequency)	Isolated	100	43	100	43	93.3	28
	Allorhythmia	81.4	35	74.4	32	63.3	19
	Couplets	58.1	25	30.2	13	13.3	4
	Triplets	25.6	11	18.6	8	6.7	2
	Unstable SVT	20.9	9	11.6	5	6.7	2
	Paroxysmal SVT	4.6	2	4.6	2	–	–
VE (registration frequency)	Isolated	72.1	31	62.5	27	20	6
	Allorhythmia	41.9	18	37.2	16	6.7	2
	Couplets	30.2	13	20.9	9	–	–
	Triplets	9.3	4	6.9	3	–	–
SVE (number/duration)	Isolated, (n)	1846.3 ± 128.6*		1321.4 ± 142.1**		328.7 ± 48.4	
	Allorhythmia, (min)	26.3 ± 2.8*		21.5 ± 3.1*		4.2 ± 0.4	
	Couplets, (n)	82.6 ± 7.4*		59.4 ± 2.3**		14.8 ± 0.6	
	Triplets, (n)	41.1 ± 3.3*		31.9 ± 1.1**		9.7 ± 0.3	
	Unstable SVT, (n)	22.8 ± 1.2*		17.7 ± 0.7**		4.4 ± 0.2	
	Paroxysmal SVT, (n)	9.7 ± 0.6*		7.3 ± 0.3**		–	
	Paroxysmal SVT, (min)	21.4 ± 3.8*		11.4 ± 2.6**		–	
VE (number/duration)	Isolated, (n)	986.2 ± 72.3*		783.9 ± 59.4**		108.4 ± 14.1	
	Allorhythmia, (min)	19.8 ± 3.6*		14.7 ± 2.7*		2.1 ± 0.4	
	Couplets, (n)	56.1 ± 2.3*		44.7 ± 1.2**		–	
	Triplets, (n)	20.5 ± 1.8*		12.4 ± 0.8**		–	
Average HR (day)	95.3 ± 2.2**		89.1 ± 2.4**		77.5 ± 0.4		
Average HR (night)	61.3 ± 1.4*		61.4 ± 1.7*		55.2 ± 0.2		
CI	155.4 ± 5.1*		148.6 ± 5.5		143.8 ± 1.3		

*: the difference is significant compared with the control group (P < 0.05); #: the difference is significant compared to before ART (P < 0.05).

Discussion

The life expectancy of human immunodeficiency virus-infected (HIV+) persons has increased due to an effective and available ART. As the HIV+ population age, HIV+ persons are experiencing an increasing burden of comorbidities, including cardiovascular diseases (CVDs) [13]. Myocardial infarction, arrhythmias, heart failure, and sudden cardiac death appear to occur more frequently in HIV+ versus non-infected persons [7,8,11]. Epidemiologic data suggest elevated risks for arrhythmias and sudden cardiac death among HIV+ persons, but clinical characteristics and mechanisms associated with these risks are not well understood [8,11]. A previous analysis of HIV+ persons in the Veterans Affairs (VA) HIV Clinical Case Registry used International Classification of Disease-9 (ICD-9) codes to identify likely AF/atrial flutter (AFL) diagnoses and found that a high HIV viral load and low CD4+ T cell count were associated with a significantly increased AF/AFL incidence [14]. However, none of the previous studies, as we know, has compared AF/AFL in HIV+ persons and uninfected controls. Similarly, although administrative codes may have a positive predictive value as low as 70 % for identifying AF, early studies, in our view, have not addressed AF/AFL diagnoses among HIV+ persons [15].

HIV-related immunosuppression (nadir CD4+ count <200 cells/mm³) and traditional CVD risk factors are associated with significantly elevated odds of AF/AFL among HIV+ persons. Although both AF and AFL were more common among HIV+ versus uninfected persons in this cohort, this

difference was attenuated by adjustment for demographics and CVD risk factors.

It was also found in a study of J. M. Sanders [16] that AF/AFL was somewhat more prevalent among HIV+ persons compared with frequency-matched controls, but that this difference was attenuated to statistical non-significance after adjustment for demographics and CVD risk factors. This may be due in part to a greater burden of co-morbidity among HIV+ persons compared with uninfected controls, as reflected in the generally sicker nature of the HIV+ persons in this cohort compared with uninfected controls frequency-matched on demographics and zip code. Nevertheless, the finding that greater progression of HIV was associated with a substantially greater likelihood of AF/AFL among HIV+ persons suggests that HIV disease-related factors may also play a role in AF/AFL [16].

Our study has revealed that in HIV-infected patients, prior to ART initiation, there was an increased sympathetic tone manifested by changes in the indicators of HR and CI towards increase. At the same time, changes in HRV were noted, in particular, a decrease in SDNN and an increase in SDANN in the absence of significant differences in other integral and time-domain parameters compared to the general population. In addition, an increased sympathetic nervous system activity was confirmed based on time-domain parameters of HRV analysis. An increase in the LF component and LF/HF ratio was noted compared with the general population.

Moreover, significantly more severe cardiac arrhythmias were registered among HIV-infected patients as shown by a

higher incidence and number of both SVE and VE, including forms which are not typical for healthy individuals.

It has been noted that in the course of effective ART, in HIV-infected patients, there was a relative normalization of HRV indices and a decrease in the incidence and severity of both SVE and VE. However, the changes achieved are not fully consistent with the results of the general population examination.

Identified results were accompanied by a decrease in hsCRP, which confirms the effect of systemic inflammation on both HRV and identified cardiac rhythm disorders.

Nevertheless, in HIV-infected patients reached the virological and immunological goals of ART, heart rhythm disturbances are not characteristic of the general population. This justifies the need to develop new approaches to the diagnosis and treatment of such patients, which will include the additional use of antiarrhythmic drugs.

Conclusions

1. In HIV-infected patients, supraventricular and ventricular ectopy are more pronounced and significantly more frequently recorded, including ectopic rhythms, which are not characteristic of healthy people.

2. In HIV-infected patients on antiretroviral therapy for 52 ± 4 weeks when viral load <20 copies/ml and CD4+ T lymphocytes >400 cells/ml are reached, the frequency of supraventricular and ventricular ectopy registration is significantly decreased but does not meet the indicators of healthy people.

3. In HIV-infected patients, a decrease in supraventricular ectopy and ventricular ectopy intensity occurs coupled with a decrease in the level of hsCRP, as well as an improvement in the integral time and spectral indices of heart rate variability. This suggests that systemic inflammatory response and hypersympathicotonia are pathogenetic links of arrhythmogenesis in HIV-infected patients.

Prospects for further research. More studies are needed to find out the prevalence of life-threatening arrhythmias in HIV-infected patients, their influence on the prognosis as well as to evaluate the effectiveness of antiarrhythmic drugs.

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Information about authors:

Kovalenko V. M., MD, PhD, DSc, Professor, Academician of the National Academy of Medical Sciences of Ukraine, Head of the Division of the Non-Coronary Heart Diseases and Rheumatology, SI "National Scientific Center "M. D. Strazhesko Institute of Cardiology" NAMS of Ukraine", Kyiv.
Vasylenko V. A., MD, PhD, Associate Professor of the Department of Pediatrics, Family Medicine and Clinical Laboratory Diagnostics FPE, SI "Dnipropetrovsk Medical Academy Ministry of Health of Ukraine", Kryvyi Rih.
Potabashnii V. A., MD, PhD, DSc, Professor, Head of the Department of Therapy, Cardiology and Family Medicine FPE, SI "Dnipropetrovsk Medical Academy Ministry of Health of Ukraine", Kryvyi Rih.

Vasylenko A. M., MD, PhD, DSc, Professor of the Department of Therapy, Cardiology and Family Medicine FPE, SI "Dnipropetrovsk Medical Academy Ministry of Health of Ukraine", Kryvyi Rih.

Відомості про авторів:

Коваленко В. М., академік НАМН України, д-р мед. наук, професор, зав. відділення некоронарних хвороб серця та ревматології, ДУ «ННЦ «Інститут кардіології імені академіка М. Д. Стражеска» НАМН України, м. Київ.
Василенко В. А., канд. мед. наук, доцент каф. педіатрії, сімейної медицини та клінічної лабораторної діагностики ФПО, ДЗ «Дніпропетровська медична академія МОЗ України», м. Кривий Ріг.
Потабашний В. А., д-р мед. наук, професор, зав. каф. терапії, кардіології та сімейної медицини ФПО, ДЗ «Дніпропетровська медична академія МОЗ України», м. Кривий Ріг.
Василенко А. М., д-р мед. наук, професор каф. терапії, кардіології та сімейної медицини ФПО, ДЗ «Дніпропетровська медична академія МОЗ України», м. Кривий Ріг.

Сведения об авторах:

Коваленко В. Н., академик НАМН Украины, д-р мед. наук, профессор, зав. отделением некоронарных заболеваний сердца и ревматологии, ГУ «УНЦ «Институт кардиологии имени академика М. Д. Стражеско» НАМН Украины, г. Киев.
Василенко В. А., канд. мед. наук, доцент каф. педиатрии, семейной медицины и клинической лабораторной диагностики ФПО, ГУ «Днепропетровская государственная медицинская академия МЗ Украины», г. Кривой Рог.
Потабашный В. А., д-р мед. наук, профессор, зав. каф. терапии, кардиологии и семейной медицины ФПО, ГУ «Днепропетровская государственная медицинская академия МЗ Украины», г. Кривой Рог.
Василенко А. М., д-р мед. наук, профессор каф. терапии, кардиологии и семейной медицины ФПО, ГУ «Днепропетровская государственная медицинская академия МЗ Украины», г. Кривой Рог.

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