
DURATION OF ABPM AS AN IMPORTANT PREREQUISITE FOR A RELIABLE DIAGNOSIS OF VASCULAR VARIABILITY DISORDERS (VVDS)

L.Z. Gumarova, G. Cornelissen, F. Halberg

Halberg Chronobiology Center
University of Minnesota
MMC 8609, 420 Delaware St. SE, Minneapolis, Minnesota, USA, 554555

A.T. Mansharipova

Kazakhstan-Russian Medical University
Torekulov str., 71, Almaty, Republic of Kazakhstan, 050004

K. Otsuka

Daini Hospital
Tokyo Women's Medical University
Medical Center East
Nishiogu 2-1-10, Arakawa, Tokyo 116, Japan

E.V. Syutkina

Institute of Pediatrics
Scientific Center for Children's Health Academy of Medical Sciences
Lomonosovsky av., 2/62, Moscow, Russia, 119991

A.V. Masalov

Optics Department
Lebedev Physical Institute
Leninsky Prospect, 53, Moscow, Russia, 119991

S.M. Chibisov, V.A. Frolov

Department of Pathological Physiology
People's Friendship University of Russia
Miklukho-Maklaya str., 6, Moscow, Russia, 117198

ABPM records from 26 clinically healthy residents of Tosa City, Japan over 6 or 7 days were analyzed overall and day-by-day in order to determine the frequency of occurrence of vascular variability abnormalities (VVAs) and the extent of reproducibility of the results from one day to another. ABPM records over 18 to 33 hours from 360 patients of a specialized cardiology clinic in Almaty (Kazakhstan) with cardiovascular diseases of medium or high severity were also analyzed.

Among all records from Tosa City, at least one VVA was found on at least one day in all residents. Twelve subjects with no overall abnormality had VVAs in 1 to 3 days. Of the remaining 14 subjects, only one had no overall abnormality but at least one VVA in 6 of 7 days. The other 13 had at least one VVA in 4 or more days as well as an overall abnormal record. One or more VVAs occurred in 78% of the cardiac patients in Almaty. More than one type of VVA was found in 50% of the patients. In 22% of cardiac patients no VVA was found, despite the fact that these patients had cardiovascular diseases. The large day-to-day variability in circadian characteristics of blood pressure and heart rate observed in Tosa City and the associated presence or absence of VVA(s) on a given day indicate the need to monitor for longer than 24 hours and to repeat the monitoring once a VVA is detected, until historically feasible lifelong monitoring can be implemented.

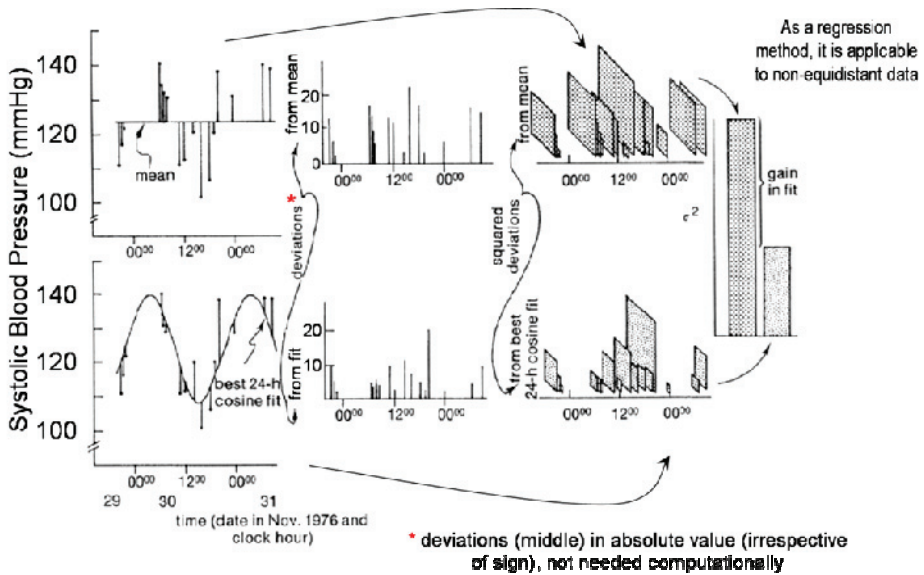
Key words: ambulatory monitoring, blood pressure, heart rate, sphygmochron, vascular variability disorders.

Automatic around-the-clock measurements of blood pressure (BP) and heart rate (HR) by ambulatory monitoring (ABPM) in clinical health served to derive time-specified reference limits computed as 90% prediction limits specified by gender and age

[1]. Data are analyzed by sphygmochron [2—4], consisting of parametric and non-parametric assessments. Parametrically, by least squares (Figure 1), a two-component model, consisting of cosine curves with anticipated periods of 24 and 12 hours, is fitted to the data (Figure 2) yielding estimates of the MESOR (M), 24-hour and 12-hour double amplitudes (2A) and acrophases (ϕ) [5—7].

Advantages of COSINOR (cosine fitting)

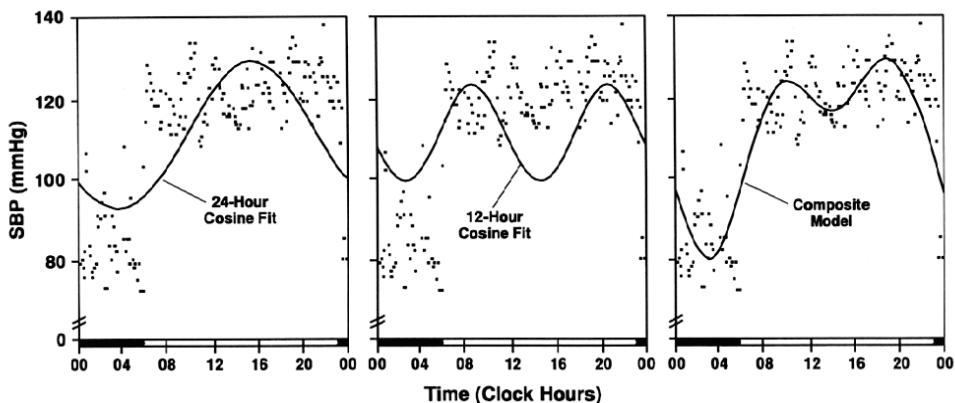
A circadian or other rhythm approximated by a 24-hour or other cosine curve (left, bottom) yields better fit than horizontal line (arithmetic mean) (left, top) gauged by reduced residual sum of squares (right)



Rhythm characteristics include a) the MESOR, more precise and more accurate than the arithmetic mean, b) the amplitude (A) and acrophase (ϕ) as additional valuable diagnosis endpoints, and c) an assessment of waveform by the (A, ϕ) pairs of harmonic terms.

Figure 1. Illustration of the principle of least squares underlying the extended cosinor method

APPROXIMATION OF CIRCADIAN WAVEFORM BY TWO-COMPONENT MODEL FITTED STEPWISE TO 24-HOUR PROFILE OF SYSTOLIC BLOOD PRESSURE (SBP) OF CLINICALLY HEALTHY MAN, 24 YEARS OF AGE*



* Each dot represents a measurement.

Figure 2. Fit of 2-component model to systolic blood pressure (SBP) data

Reference limits, also computed as 90% prediction limits separately for men and women of different age groups are derived for M , $2A$ and ϕ from records in clinical health. This model usually provides a good approximation of the decrease during rest, the small increase around mid-sleep followed by a more rapid increase around awakening, a post-prandial dip that is more accentuated with increasing age, and the evening slower decrease (Figure 3) [8].

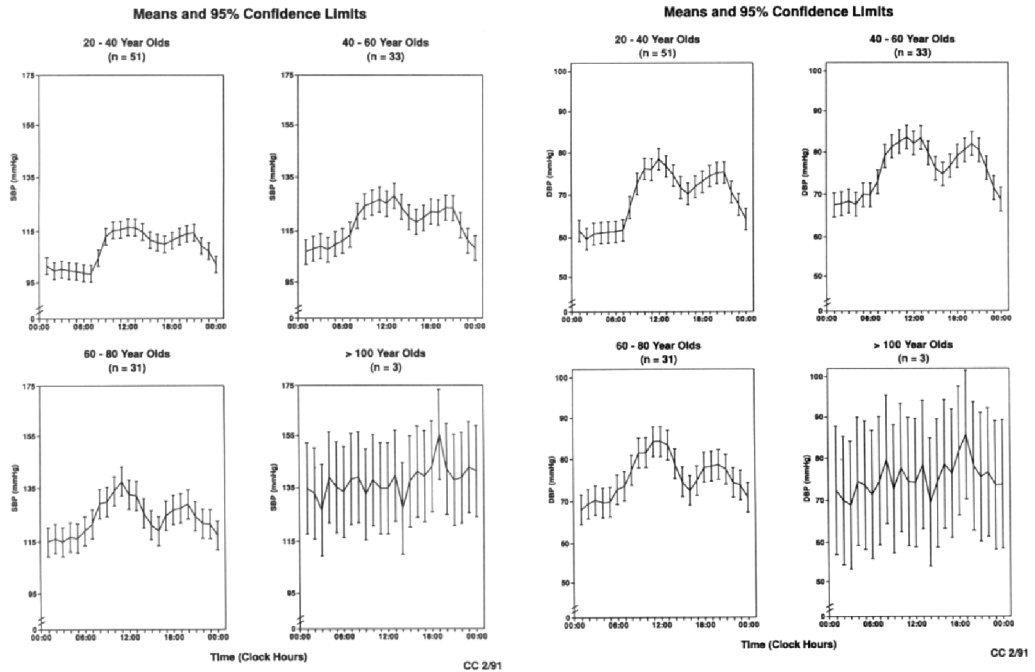


Figure 3. Circadian waveform of systolic (left) and diastolic (right) blood pressure in four age groups

NONPARAMETRIC APPROACH TO DEVIANT BLOOD PRESSURE

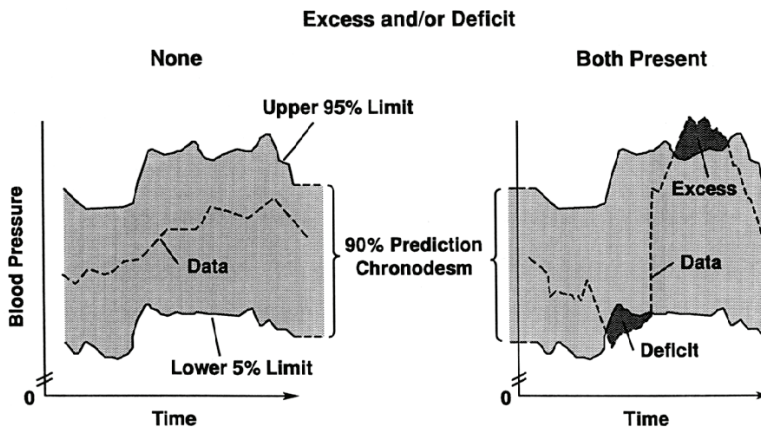


Figure 4. Nonparametric approach to blood pressure assessment

Non-parametrically, percentage time elevation, area of excess and timing of largest excess are determined by numerical integration (Figure 4). In addition to MESOR-hypertension, deviations from these chronobiological norms lead to diagnoses of CHAT and/or ecphasia when the 24-hour BP-2A is excessive and/or the 24-hour BP- ϕ is outside acceptable limits but the 24-hour HR- ϕ is acceptable. These conditions along with an excessive pulse pressure (above 60 mmHg) and a deficient HR variability (standard deviation of HR < 7.5 beats/min) constitute Vascular Variability Anomalies (VVAs) when present during one or a few days, or Vascular Variability Disorders (VVDs) when the abnormalities are confirmed over repeated week-long records in the absence of a persisting load [4]. Any two or more coexisting VVDs are referred to as Vascular Variability Syndromes (VVSs).

Table 1

Number of days with at least one VVA will have to be complemented by the extent of severity of VVA(s) each day and overall *

N of days with a VVA	N of subjects	VVA in weeklong record?		Comments
		No	Yes	
0	0			
1	3	3	0	
2	7	7	0	
3	2	2	0	
4	6	4	2	1 VVA each (S-CHAT)
5	4	2	2	1 D-MH; 1 S-&D-CHAT
6	1	1	0	
7	3	0	3	1 S-CHAT; 2 with 3 VVAs**

* One can have 6 days with a VVA and no abnormality in the overall record (row 7), a finding suggesting that the duration of a VVA is an incomplete measure, the extent of abnormality also in need of being assessed. Continuous recording with automatic analyses carried out both day-to-day and week-to-week is recommended in any event once a validated, unobtrusive monitor is miniaturized and rendered affordable in a chronobiologic system subservient to health monitoring, including mental and other strain assessment, with dividends for medical research and for monitoring effects of natural environmental factors, including solar activity.

** 1 with S-MH, EPP and S-CHAT and 1 with S-MH, EPP and DHRV. VVA: Vascular Variability Anomaly; S — (Systolic); D — (Diastolic); MH: MESOR-Hypertension; CHAT Circadian Hyper-Amplitude-Tension; EPP: Excessive Pulse Pressure (> 60 mm Hg); DHRV: Deficient Heart Rate Variability (standard deviation of HR < 7.5 beats/minute).

ABPM records from 26 residents (4 men and 22 women 39—74 years of age) of Tosa City, Japan over 6 or 7 days (2 and 24 profiles, respectively) were analyzed overall and day-by-day in order to determine the frequency of occurrence of abnormalities and the extent of reproducibility of the results from one day to another. Among all 26 records, at least one VVA is found on at least one day in all residents. Twelve subjects with no overall abnormality had a VVA in 1 to 3 days. Of the remaining 14 subjects, only one had no overall abnormality but at least one VVA in 6 of 7 days. Her data are plotted as a function of time in Figure 5, with an indication of VVAs detected on a daily basis. Her overall sphygmochron and circadian profiles of systolic and diastolic BP are shown in Figure 6. The other 13 had at least one VVA in 4 or more days as well as an overall abnormal record, Table 1. The 3 individuals with abnormality on all 7 days also have an abnormal 7-day record, one with only systolic CHAT, the other two with 3 VVDs, including systolic MESOR-Hypertension and an excessive pulse pressure together with either systolic CHAT or deficient HR variability, Table 1.

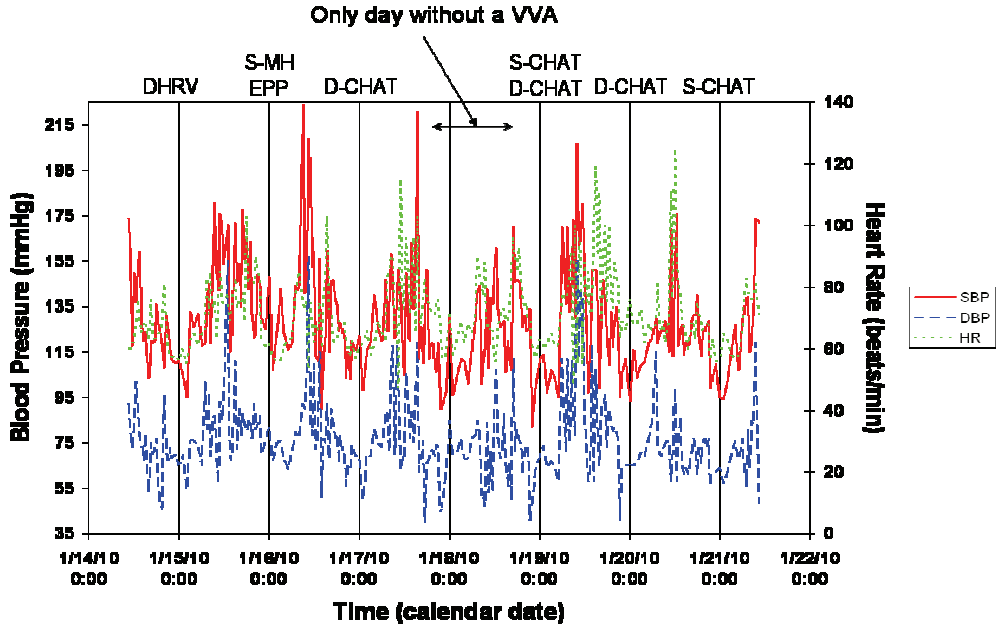


Figure 5. Day-to-day variability in BP and HR behavior. In this record, there is at least one VVA on 6 of 7 days. The overall summary shows all endpoints to be within acceptable limits (Fig. 6).

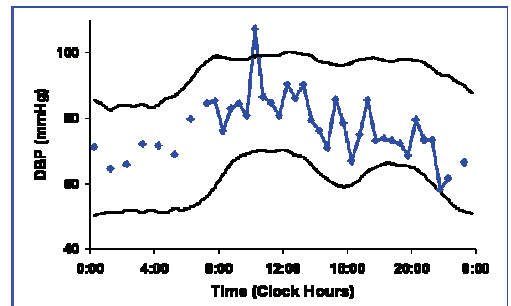
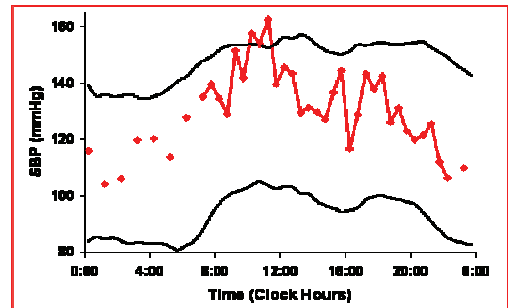
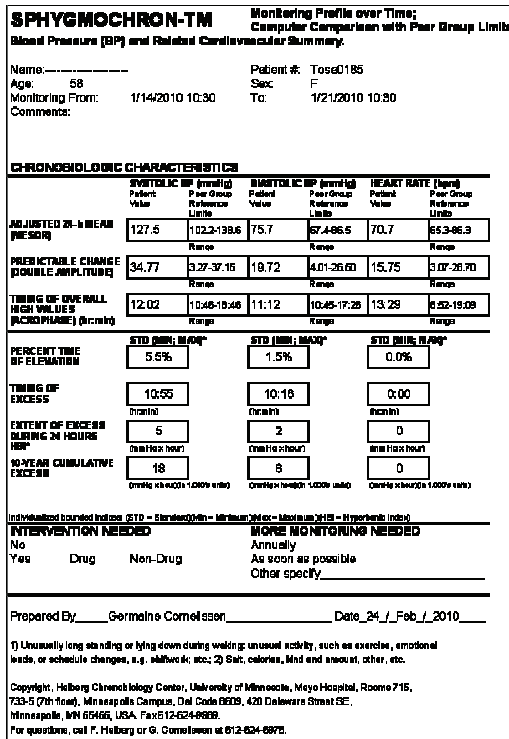


Figure 6. Overall sphygmochron of subject whose data are shown in Figure 5. Stacking of the systolic and diastolic BP data in the light of reference limits reveals only minor BP excess

The number of abnormal days in a weeklong record as such does not tell whether the 7-day record is also abnormal, a finding suggesting that the duration of a VVA is an incomplete measure, to be complemented by information on the extent of abnormality. Weeklong records were found to be abnormal in over 25% of the residents, a reason for recommending a follow-up 7-day profile once abnormality is detected in the first 7-day record, yet week-to-week variability underscores the need for unobtrusive, affordable instrumentation for continued monitoring of mental strain, gauged by VVAs.

Among treated cardiac patients in Almaty, 22% of patients had no VVA, whereas 50% had multiple VVAs. Outcome studies have shown that cardiovascular disease risk increases with the presence of each additional VVA [3, 4, 8, 9]. It is thus critical to be able to reliably detect the presence of VVAs so that non-drug or drug intervention can not only lower an elevated blood pressure but also restore healthy circadian variability patterns of blood pressure and heart rate. To do this, monitoring over spans longer than 24 hours is needed, with the further recommendation to repeat a 7-day profile once abnormality is detected. Particularly in the case of cardiac patients in need of treatment, repeated if not continuous monitoring is advocated as a means of self-surveillance, so that any undesirable change in blood pressure and/or heart rate variability can promptly be addressed. What may appear as utopia to some physicians is routine pressure measurement in the tires of some cars. The technology is available. Why do not use it in those who do and do not drive cars? The answer depends on the demand of the readers.

REFERENCES

- [1] *Nelson W., Cornelissen G., Hinkley D., Bingham C., Halberg F.* Construction of rhythm-specified reference intervals and regions, with emphasis on “hybrid” data, illustrated for plasma cortisol // *Chronobiologia*. — 1983. — V. 10. — P. 179—193.
- [2] *Cornelissen G., Otsuka K., Halberg F.* Blood pressure and heart rate chronome mapping: a complement to the human genome initiative // In: Otsuka K., Cornelissen G., Halberg F. (Eds.) *Chronocardiology and Chronomedicine: Humans in Time and Cosmos*. — Tokyo: Life Science Publishing, 1993. — P. 16—48.
- [3] *Cornelissen G., Halberg F., Bakken E.E. et al.* 100 or 30 years after Janeway or Barter, Health-watch helps avoid “flying blind” // *Biomed & Pharmacother.* — 2004. — V. 58 (Suppl 1). — S69—S86.
- [4] *Halberg F., Cornelissen G., Otsuka K. et al.* Extended consensus on means and need to detect vascular variability disorders (VVDs) and vascular variability syndromes (VVSs) // *Intl. J. of Geronto-Geriatrics*. — 2008. — V. 11. — P. 119—146. URL: http://www2.hu-berlin.de/leibniz-sozietat/journal/archiv_5_09.html
- [5] *Halberg F.* Chronobiology: methodological problems // *Acta Med Rom.* — 1980. — V. 18. — P. 399—440.
- [6] *Cornelissen G., Halberg F.* Chronomedicine // In: Armitage P., Colton T. (Eds.) *Encyclopedia of Biostatistics*, 2nd ed. Chichester, UK: John Wiley & Sons Ltd. 2005. — P. 796—812.
- [7] *Refinetti R., Cornelissen G., Halberg F.* Procedures for numerical analysis of circadian rhythms // *Biological Rhythm Research*. — 2007. — V. 38. — P. 275—325. <http://dx.doi.org/10.1080/09291010600903692>
- [8] *Cornelissen G., Chen C.H., Bingham C., Singh R.B., Halberg F.* Blood pressure overswinging (CHAT) and ecpasia (odd timing): opportunity of detecting pre-hypertension worldwide // *World Heart Journal*, in press.
- [9] *Halberg F., Cornelissen G., Halberg F., Kessler T., Otsuka K.* Measuring mental strain by duration of blood pressure overswing (CHAT): Case report // *World Heart Journal*. — 2010. — V. 2. — P. 141—167.

ПРОДОЛЖИТЕЛЬНОСТЬ МОНИТОРИРОВАНИЯ АРТЕРИАЛЬНОГО ДАВЛЕНИЯ КАК ВАЖНАЯ СОСТАВЛЯЮЩАЯ НАДЕЖНОЙ ДИАГНОСТИКИ НАРУШЕНИЙ ВАРИАбельНОСТИ ГЕМОДИНАМИЧЕСКИХ ПОКАЗАТЕЛЕЙ

Л.Ж. Гумарова, Ж. Корнелиссен, Ф. Халберг

Хронобиологический центр Халберга
Университет Миннесоты
MMC 8609, 420 Delaware St. SE, Minneapolis, Minnesota, USA, 55455

А.Т. Маншарипова

Казахстанско-Российский медицинский университет
ул. Торекулова, 71, г. Алматы, Республика Казахстан, 050004

К. Отсука

Токийский женский медицинский университет
Медицинский восточный центр
Нишиогу 2-1-10, Аракава, Токио, 116, Япония

Е.В. Сюткина

Институт педиатрии научно-исследовательского центра здоровья детей РАМН
Ломоносовский проспект, 2/62, Москва, Россия, 119991

А.В. Масалов

Физический институт им. П.Н. Лебедева, РАН
Ленинский проспект, 53, Москва, Россия, 119991

С.М. Чибисов, В.А. Фролов

Российский университет дружбы народов
ул. Миклухо-Маклая, 6, Москва, Россия, 117198

Были проанализированы данные мониторинга АД и ЧСС у 26 практически здоровых людей (4 мужчин и 22 женщин в возрасте 39—74 лет, проживающих в городе Тоса, Япония). Данные собраны на протяжении 6 суток (в 2 случаях) или 7 суток (в 24 случаях) и анализировались в целом и по отдельным суткам с целью определения частоты появления аномалий вариабельности гемодинамических показателей (АВГП) и степени воспроизводимости результатов от одного дня к другому. Для сравнения были проанализированы также записи СМАД продолжительностью 18—33 часа 360 пациентов специализированной кардиологической клиники г. Алматы (Казахстан) с заболеваниями сердечно-сосудистой системы средней и высокой степени тяжести.

Среди всех 26 записей из города Тоса по крайней мере одна АВГП обнаружена как минимум в один из дней у всех испытуемых. У двенадцати человек, не имевших отклонений суммарных показателей, в одной—трех суточных записях были обнаружены АВГП. Из оставшихся 14 пациентов только одна женщина не имела отклонений при анализе регистрограммы в целом, но у нее наблюдались не менее одной АВГП в течение 6 из 7 суток мониторинга. У остальных 13 человек с отклонениями суммарных показателей обнаружено по меньшей мере по одной АВГП в течение 4 дней и более. Одна или более АВГП отмечены у 78% кардиологических больных в г. Алматы. У 50% этих больных наблюдалось более одного типа АВГП. Примечательно, что в 22% случаев у кардиологических больных не выявлено АВГП при мониторинге указанной длительности. Высокая вариабельность циркадианных характеристик АД и ЧСС от одних суток к другим у здоровых людей, приводившая к появлению у них в некоторые дни АВГП, а также отсутствие АВГП у 22% кардиологических больных при небольшой продолжительности мониторинга указывают на необходимость проводить мониторинг длительностью более 24 часов и повторять его в случае выявления АВГП.

Ключевые слова: амбулаторный мониторинг артериального давления, частоты сердечных сокращений, вариабельность сосудистых расстройств.