

NONLINEAR RELATION OF THE CIRCADIAN BLOOD PRESSURE AMPLITUDE TO CARDIOVASCULAR DISEASE RISK

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Abstract

Data from two independent studies are reanalyzed to determine how the MESOR and the circadian amplitude (A) of blood pressure (BP) as well as the 24-hour standard deviation (SD) of heart rate (HR) relate to vascular disease risk. In one prospective study, risk is quantified by the actual number of events that occurred within 6 years. In the other retrospective study, the left ventricular mass index (LVMI) was used as a surrogate outcome measure available for all subjects. The BP MESOR is found to be linearly related to risk. By contrast, the circadian BP-A and the 24-hour SD of HR show a nonlinear relation with risk, which is elevated only after a threshold value for BP-A or HR-SD is exceeded. For the diagnosis of a deviation in BP and HR, the recommendation to monitor for 7 days at the outset seems as reliable an assessment as practical, but it may not be sufficient, and the patient must be advised that further monitoring may be needed.

Key words:

Cardiovascular disease risk, circadian blood pressure amplitude, essential hypertension

INTRODUCTION

As documented longitudinally in the Framingham study (1), vascular disease risk increases linearly with an increasing mean value of BP. A great vascular disease risk elevation is also associated with an excessive circadian BP amplitude (CHAT, brief for **c**ircadian **h**yper**a**mpli**t**ude**t**ension) (2, 3, 4, 5). Independent studies relying on the 24-hour SD of BP also support the increase in vascular disease risk associated with too much BP variability (6). The increase in cardiovascular disease risk associated with a decreased HR variability has also been recognized (7-10). Too low a SD of HR is one of several **chr**ome alterations of **h**eart **r**ate **v**ariability (CAHRVs).

Multiple regression analyses are often the method of choice to identify risk factors. Such methods are well suited when dealing with factors that relate linearly with risk but are likely to fail to show any association if a nonlinear relation prevails. Against this background, results from two independent studies are re-examined herein to assess the relationship of the BP-MESOR and of two dynamic endpoints, namely the circadian BP-A and the 24-hour HR-SD, to vascular disease risk.

SUBJECTS AND METHODS

One data set stems from a 6-year prospective study of 297 patients without any vascular complication at the start of study (121 MESOR-normotensive subjects and 176 treated MESOR-hypertensive patients). At the start of study, each patient provided a 48-hour profile of BP and HR measurements at 15-min intervals obtained around the clock with an ambulatory monitor (2). The incidence of coronary artery disease, cerebral ischemic events, nephropathy and retinopathy was recorded at 6-month intervals for 6 years. The other data set stems from a study of 424 patients in Taiwan (3). Each provided a 24-hour profile of BP and HR measurements and an echocardiogram for the determination of the left ventricular mass index (LVMI).

For each data set, the subjects were subdivided in several categories according to the MESOR of their systolic (S) and diastolic (D) BP, according to the circadian amplitude of their SBP and DBP, and according to the 24-hour SD of their HR. The incidence of adverse events in each class was determined and compared to the adjacent class by chi-square. The mean LVMI values were compared between adjacent classes by Student t-test.

RESULTS

The incidence of adverse vascular events was about 10% (28 cases) in patients with an acceptable circadian BP amplitude, whereas it was 44% (11 cases) in patients with diastolic CHAT ($P < 0.001$ by χ^2 test). LVMI is found to be elevated in MESOR-hypertensive vs. MESOR-normotensive patients, and to increase both as a function of age and as a function of the squared magnitude of BP ($P < 0.05$). In both studies, the relation between vascular disease risk and the circadian BP amplitude (or magnitude, when assessed by the cosinor fit of more than one component) is nonlinear. Whereas risk progressively increases for increasing 24-hour mean values of BP, the circadian amplitude has to exceed a threshold for an increase in risk to occur (*Figs. 1 and 2*). A similar result applies for the 24-hour SD of HR (*Fig. 3*). The fact that there is no statistically significant correlation between the BP-A and the 24-hour SD of HR (*Fig. 4*) suggests that CHAT and CAHRV are two different disease risk syndromes.

DISCUSSION

As apparent from *Figs. 1-3*, the risk of adverse vascular events increases linearly with progressively increasing mean values of BP. By contrast, there is no change in risk for a wide range of circadian amplitudes of BP, or of 24-hour SDs of HR, but when these dynamic endpoints exceed a threshold, the risk is drastically and statistically significantly increased, suggesting a nonlinear relation with risk. The same relationship is found in two different studies, one carried out

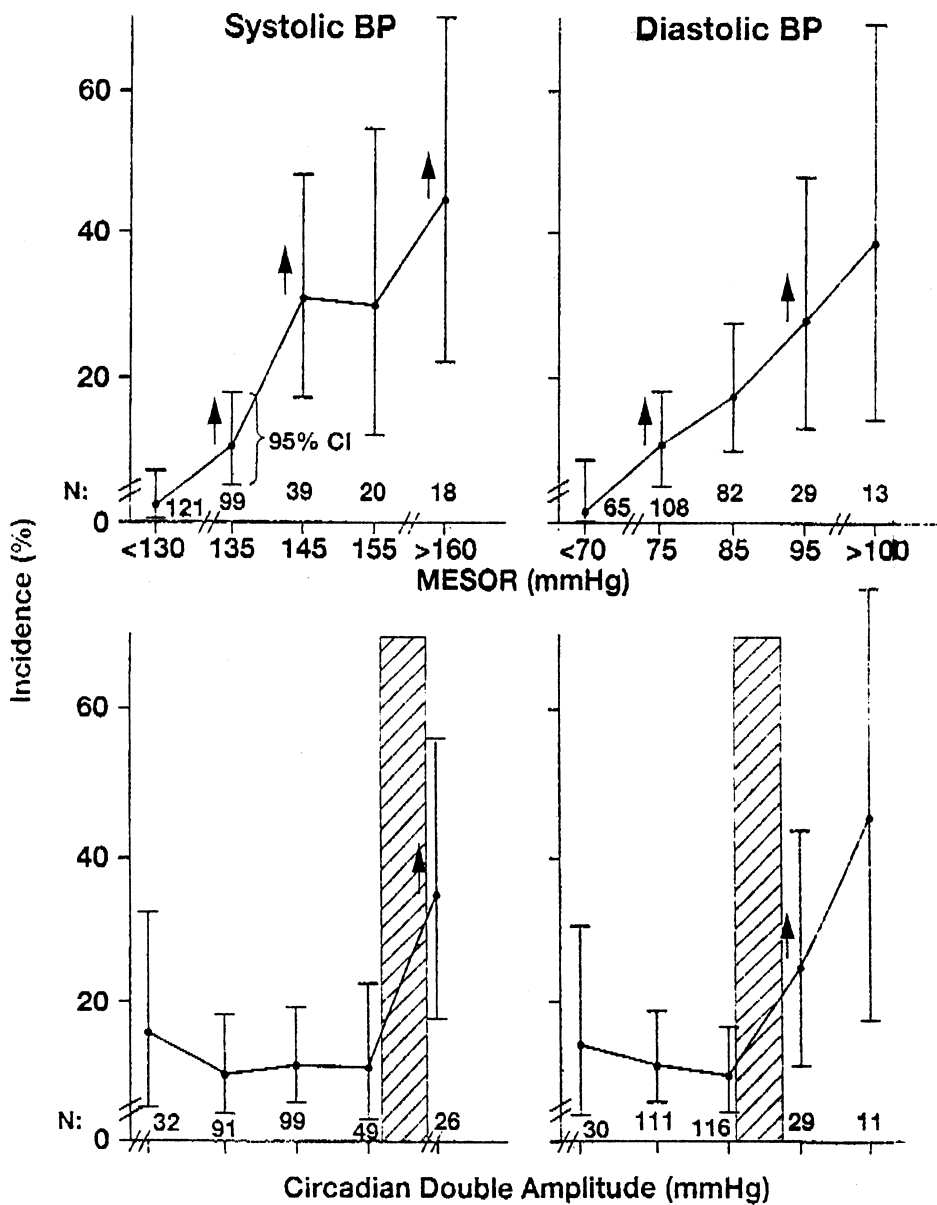


Fig. 1.

Threshold (hatched; bottom) must be exceeded before the circadian double amplitude (2A) of blood pressure (BP) indicates a disease syndrome; the BP - 2A relates nonlinearly to vascular disease incidence, the 24-hour mean (MESOR; top) does so nearly linearly

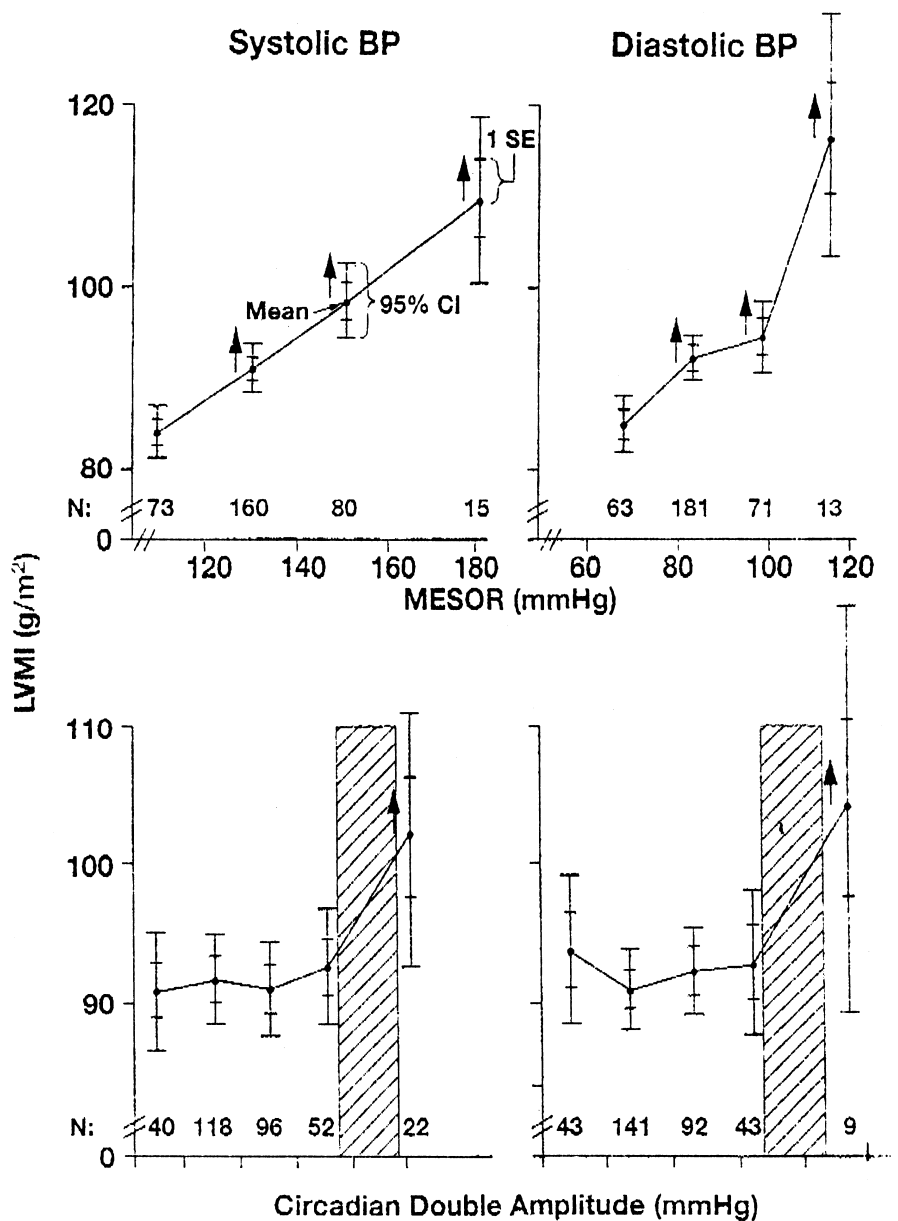


Fig. 2.

Threshold (hatched; bottom) must be exceeded before the circadian double amplitude (2A) of blood pressure (BP) indicates a disease risk syndrome; the BP - 2A relates nonlinearly to the left ventricular mass index (LVMI), the 24-hour mean (MESOR; top) does so nearly linearly

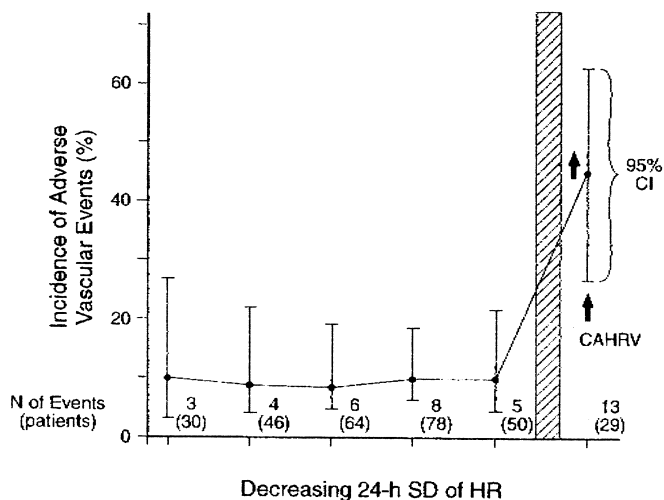


Fig. 3.

Threshold (hatched) must be exceeded before 24-hour standard deviation (SD) of the heart rate (HR)* indicates a disease risk syndrome (CAHRV)** the HR-SD relates nonlinearly to the incidence of adverse vascular events

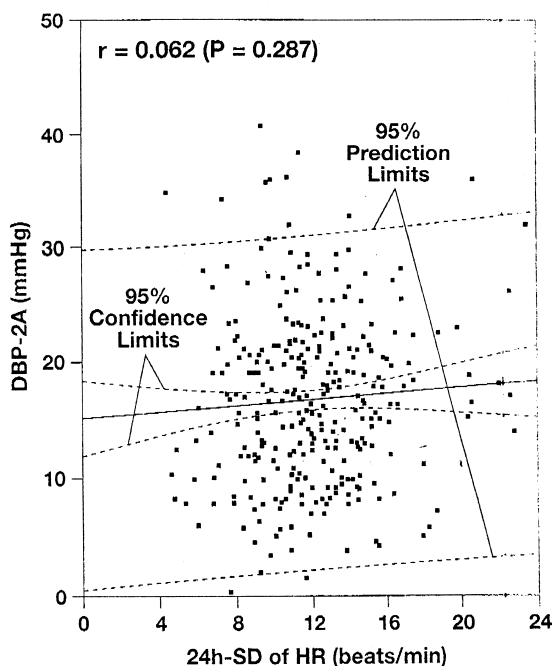


Fig. 4.

Apparently different risks assessed by measures of CHAT (ordinate) and a CAHRV (ABSCISSA)*

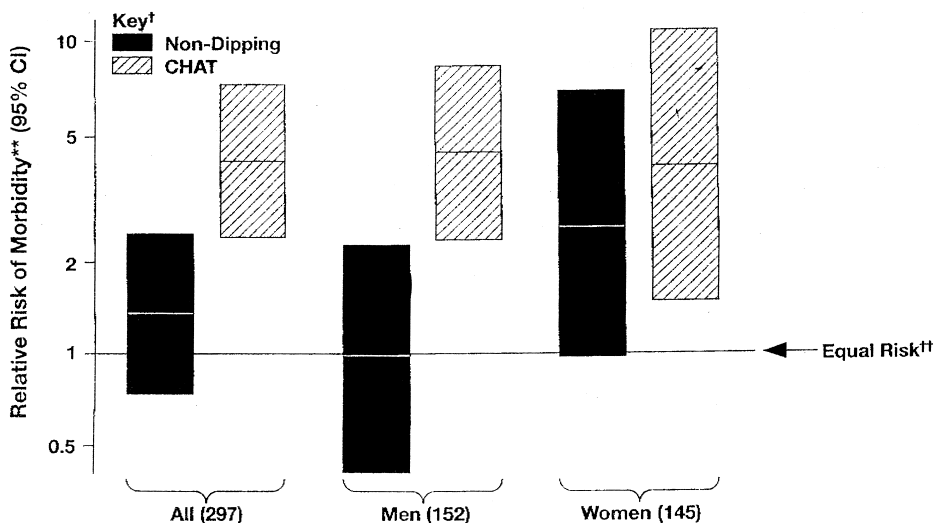


Fig. 5.
Circadian hyper-amplitude- tension (CHAT) affects men and women, „non-dipping“ may affect women*

prospectively, the endpoint being the actual incidence of morbid events, the other study being a retrospective analysis of data wherein the LVMI is used as a surrogate outcome measure available for each patient.

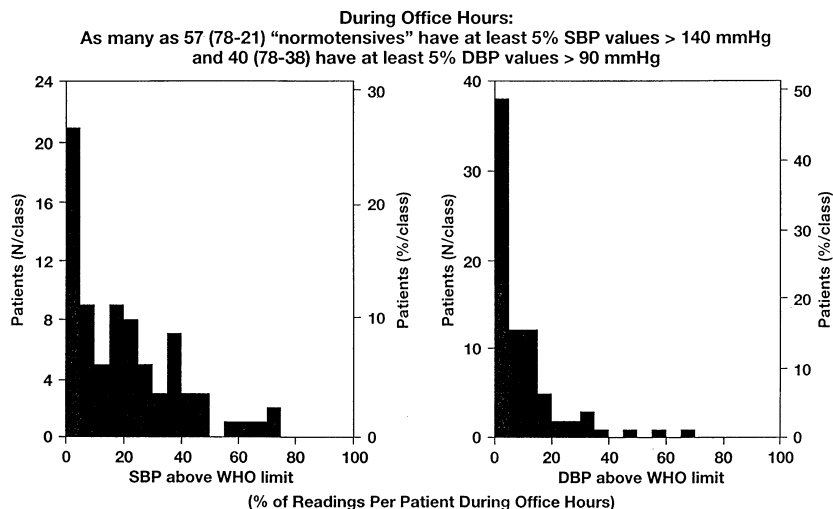
Fig. 5 shows that CHAT is a risk factor that applies equally to men and women. By contrast, a gender difference characterizes the increase in risk associated with „non-dipping“ (11, 12), the condition of a very small circadian amplitude of BP. In Fig. 5, the incidence of adverse vascular events is compared between „non-dippers“ and „dippers“ and between patients with „CHAT“ vs. patients with an acceptable circadian BP amplitude. Whereas CHAT is invariably associated with a statistically significant increase in risk, the risk of „non-dippers“ does not differ with statistical significance from the risk of „dippers“ in the overall population or in men, but it tends to do so for women, as can be seen from the only slight overlap by the 95% confidence interval of a relative risk of one, the latter representing equal risk between „dippers“ and „non-dippers“. This result suggests that a very small circadian amplitude of BP may also be associated with

vascular problems in women, whereas CHAT remains the largest risk factor assessed thus far for both men and women (2, 13).

The fact that a deviant circadian BP pattern can predict vascular disease risk has several implications. First, there is merit in assessing the dynamic changes in BP, even when they occur within the physiological range, since endpoints such as the circadian amplitude are informative from a clinical viewpoint. Second, spotchecks of BP in patients with CHAT are likely to result in inadequate decisions to treat or not to treat (14). Third, the current guidelines for screening and diagnosis (15) are inadequate to identify patients with CHAT, who may be at an even higher vascular disease risk than patients with MESOR-hypertension (14, 16). Fourth, BP should be measured more than once, preferably systematically around the clock for at least 7 days, to reliably assess the circadian variation and, in certain cases, a one-week record is not conclusive (17, 18, 19).

The dangers of misdiagnosis based on single BP measurements are illustrated in Figs. 6-8. Patients conventionally diagnosed either as „normotensive“ or „hypertensive“ were monitored ambulatorily for 7 days. Their daytime measurements were examined to determine the proportion of values above or below currently used WHO standards found during office hours. The number of patients in classes with different percentages of readings above or below WHO limits, respectively, are shown as histograms in Figs. 6 and 7. During office hours, as many as 57 of 78 „normotensives“ (>70%) have at least 5% SBP values above 140 mm Hg and 40 (50%) have at least 5% DBP values above 90 mm Hg. Among the „hypertensive“ patients, during office hours, as many as 38 (>80%) have at least 5% SBP values below 140 mm Hg and all 45 patients have at least 5% DBP values below 90 mm Hg. About 50% discrepancy in diagnosis accuracy is no better than flipping a coin !

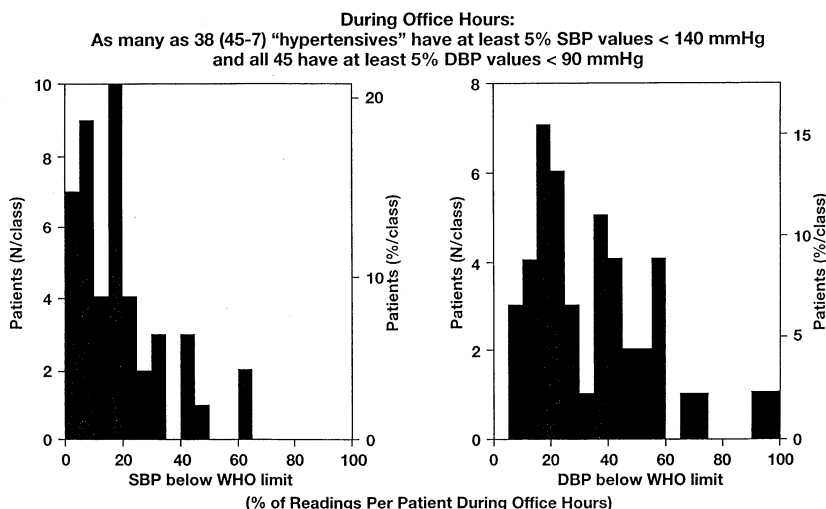
A similar conclusion is reached from another study relying on 66 ambulatory BP profiles spanning 7 days or longer from subjects 14-106 years of age. The chronobiologic diagnosis based on the whole profile was compared to that based on successive single 24-hour profiles, the current „gold standard“. From day to day there is good overall agreement for the MESOR of HR, the diagnosis based on all single 24-hour profiles being the same as that based on the whole 7-day profile in 64 of 66 cases (97.0%). By comparison, full agreement for the BP MESOR is only 87.9% for DBP and 74.2% for SBP. In other words, in the latter case, a diagnosis based on a single 24-hour profile can be discrepant at least once (in 7 days) in 25% of the cases. Much worse is the situation concerning a decision of acceptability for the circadian BP (or HR) amplitude: full agreement is only found in 37.9% of the 66 one-week profiles for SBP, 63.6% for DBP and 66.7% for HR. This status quo is not desirable when an excessive circadian BP amplitude has been shown to carry a large increase in risk of ischemic stroke and other adverse vascular complications.



*Determined on the basis of 7-day records obtained by ambulatory monitor (ABPM-630 from Colin Medical Instruments, Komaki, Japan); histogram class width is 5% (of office-hour readings).

Fig. 6.

Distribution of systolic (S, left) and diastolic (D, right) blood pressures (BP) above who limits (140/90 mmHg) observed during daytime (08:00-17:00) in 78 patients conventionally diagnosed as normotensive*



*Determined on the basis of 7-day records obtained by ambulatory monitor (ABPM-630 from Colin Medical Instruments, Komaki, Japan); histogram class width is 5% (of office-hour readings).

Fig. 7.

Distribution of systolic (S, left) and diastolic (D, right) blood pressures (BP) above who limits (140/90 mmHg) observed during daytime (08:00-17:00) in 45 patients conventionally diagnosed as hypertensive*

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NELINEÁRNÍ VZTAH MEZI CIRKADIÁNNÍ AMPLITUDOU KREVNIHO TLAKU A RIZIKEM KARDIOVASKULÁRNÍCH ONEMOCNĚNÍ

S o u h r n

Údaje ze dvou nezávislých studií byly znovu analyzovány, abychom zjistili vztahy MESORU, cirkadiánní amplitudy krevního tlaku a 24-hodinové směrodatné odchylky srdeční frekvence k míře rizika kardiovaskulárních onemocnění. V jedné prospektivní studii jsou rizika kvantifikována skutečným počtem událostí, které se vyskytly v průběhu šesti let. V druhé retrospektivní studii jsme použili index masy levé komory jako výstupní hodnotu, dostupnou u všech vyšetřených. Zjistili jsme, že MESOR krevního tlaku a rizika jsou v lineární závislosti. Naopak cirkadiánní amplituda krevního tlaku a směrodatná odchylka srdeční frekvence za 24 hodin jsou v nelineárním vztahu k rizikům, která se zvyšují až po překročení prahové hodnoty amplitudy krevního tlaku nebo směrodatné odchylky srdeční frekvence. Sedmidenní monitorování krevního tlaku a srdeční frekvence na počátku diagnostiky se zdá být spolehlivým hodnocením, nemusí být však dostačující a v některých případech může být potřebné další monitorování.

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