Long-Term Stability of Cardiovascular and Catecholamine Responses to Stress Tests
An 18-Year Follow-Up Study

Skjalg S. Hassellund, Arnljot Flaa, Leiv Sandvik, Sverre E. Kjeldsen, Morten Rostrup

Abstract—Cardiovascular (CV) hyperreactivity to stress must be reasonably stable if it is considered to be important in the development of hypertension and CV disease. The aim of the present study was to assess long-term stability of blood pressure, heart rate, epinephrine, and norepinephrine responses to a cold pressor test and a mental arithmetic stress test. Eighty-one subjects selected from the first (n=30), 50th (n=30), and 95th to 99th (n=39) percentiles of the mean blood pressure distribution at a military draft procedure were tested on 2 occasions 18 years apart. Stress responses were measured during a cold pressor test (hand immersed in ice water for 1 minute) and during a mental stress test (subtraction for 5 minutes). Intra-arterial blood pressure measurements and arterial catecholamine samples were taken at the initial examination. At follow-up, noninvasive Finapres beat-to-beat blood pressure measurements and venous plasma catecholamine samples were used. The 18-year correlations of the CV and epinephrine absolute responses during mental stress ranged from 0.6 to 0.8. The entry/follow-up correlation of systolic blood pressure during the mental stress test (95% CI: 0.69 to 0.86) was significantly higher than during the cold pressor test (95% CI: 0.30 to 0.65), and responses to mental stress overall appeared to be more stable than responses to the cold pressor test. Our study suggests that CV and sympathoadrenal reactivity, specifically to mental stress, are relatively stable individual characteristics. These results support one of the necessary preconditions to consider hyperreactivity involved in the development of hypertension and CV disease. (Hypertension. 2010;55:131-136.)

Key Words: physiological stress reactivity ■ stability ■ cold pressor test ■ mental stress ■ epinephrine ■ norepinephrine ■ blood pressure

The reactivity hypothesis suggests that subjects with an exaggerated response to stress are at risk of later developing hypertension and cardiovascular (CV) disease. The validity and the importance of the hypothesis have been discussed extensively for some decades. According to Treiber et al., there is reasonable evidence to suggest that CV reactivity can predict the development of some preclinical states, that is, hypertension and left ventricular hypertrophy. To consider hyperreactivity as a contributing factor in the development of CV diseases, an important precondition needs to be addressed; the reactivity of an individual must show a reasonable stability in the long term.

A meta-analysis from 1996 summarizing important test-retest studies assessing reactivity found mean Pearson correlation r values of heart rate to equal 0.56, whereas it was 0.41 for systolic and 0.35 for diastolic blood pressures (BPs). Most of the studies included were on the basis of test-retest intervals of days to months, and there were few studies with intervals of more than a year. They concluded that the reproducibility of systolic BP and heart rate declined as the test-retest interval increased, questioning the importance of hyperreactivity as a risk factor for CV diseases.

In most test-retest studies, CV measures like BP and heart rate have been investigated. The study with the longest test-retest interval was a 10-year follow-up reporting Spearman correlations in the range of 0.20 to 0.59. Some studies have tried to pinpoint the underlying influence of the autonomic nervous system on CV reactivity by assessing, for example, respiratory sinus arrhythmia and plasma catecholamines. So far the longest previous test-retest period reported assessing catecholamine reactivity was 1 year.

The present study is the first to present data on the long-term stability of catecholamine responses to stress tests and also the first to assess the stability of CV reactivity with a test-retest period as long as 18 years.

Methods

The local ethics committee approved the study, and the procedures followed were in accordance with institutional guidelines. Written, informed consent was obtained from each subject both at the initial examination and at follow-up. The study adhered to the principles of the Declaration of Helsinki and Title 45 of the US Code of Federal Regulations (part 46, Protection of Human Subjects, revised November 13, 2001, effective December 13, 2001).

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Participants
All of the 19-year–old men in Norway have to attend a medical examination for the military draft procedure. BP measurements were undertaken by a trained physician once after 5 minutes of sitting by means of a carefully validated automatic auscultatory device (Boso digital II S, Bosh & Sohn GmbH u Co) or by using a mercury sphygmomanometer. None of the subjects were informed about the BP at this stage. Mean BP was calculated as diastolic BP plus pulse pressure divided by 3.

Several articles have been published on subjects selected from these BP measurements.8–11 Participants of the current study largely constitute the same participants, but they also had to fulfill 2 additional criteria: unawareness of screening BP and satisfactory intra-arterial BP measurements or satisfactory catecholamine samples. Of 7984 men attending the military draft screening, a total of 99 were included in the current study, 30 belonging to the first, 30 to the 50th, and 39 to the 95th to 99th percentiles of the mean BP distribution. This selection was initially done to ensure a satisfying sympathetic function and coronary risk factors.9 All were white except 1 who was half Asian. They were previously healthy without any history of diabetes mellitus, renal disease, increased BP, or other CV diseases, including a normal physical examination, ECG, routine blood tests, and urine analysis. None were on medical treatment or abused drugs or alcohol.

Follow-up examinations were conducted from February 2005 to September 2006. The average time of follow-up was 18.0±0.9 years. Eighty one (82%) of the original 99 subjects were available. A total of 6 were not re-examined, that is, 1 was excluded because of suspected intravenous drug addiction, 2 lived abroad and were not able to attend, 4 did not answer any letters or calls, and 11 did not want to participate. There were no significant differences in initial resting BP, heart rate, body mass index, fasting plasma glucose concentration, or catecholamine stress responses between those who met for the follow-up and the others. One of the subjects who were re-examined had ulcerative colitis and was excluded from data analyses because of colectomy with instructions to ingest excess amounts of water and salt.

Procedures
The protocol applied at the initial examination has been described in detail elsewhere10 and took place between October 1986 and October 1989. All of the participants received a written invitation to take part in the study examining their stress responses without any information about their resting BP. All of the subjects were examined by the same physician, and there was only 1 subject each day. The participants and the physician were unaware of which of the selection groups the subject belonged to. Examinations started at 8:00 AM each day. They fasted and were instructed to abstain from any medication or smoking for the preceding 8 hours and from alcohol the preceding 24 hours before examination. The examining physician was unaware of the individual results of the initial examination. A basic clinical examination and standardized questionnaires were used to collect information about health status, comitant diseases, medication, and family history.

The conduction and duration of the stress tests and the periods of rest before, between, and after the stress tests were the same. However, there were some changes in the follow-up examination. Because of the invasiveness of an intra-arterial catheter, a noninvasive Finapres beat-to-beat BP monitor was used during the stress tests. The catecholamine samples were, therefore, not taken arterially but from a catheter positioned in the left cubital vein. There was only 1 catecholamine sample taken at the end of the CPT. To reduce the chance that high correlations were partly attributable the excitement related to the MST, because this was the first test conducted on the first occasion, the order was reversed at the follow-up examination. At follow-up, systolic and diastolic BPs during the stress tests were measured noninvasively by a Finometer (Finapres Medical System) that was connected to BeatScope (BeatScopeH, Finapres Medical System) software. Heart rate was measured by the Mingograph used at the initial examination and was connected to the Finapres monitor. Standard venous catheters were used to obtain venous blood samples, and they were handled and analyzed as during the initial examination.

The CV variables at entry were calculated manually on the basis of continuous BP and ECG recordings. BP and heart rate were generally derived from periods closely related to the collection of catecholamines at all of the stages of the tests. During the MST, three 8-second sequences of heart rate and BP were determined after 1, 3, and 5 minutes and, during the CPT, 2 sequences after 30 seconds and 1 minute were used. In the follow-up analysis, the CV variables were calculated automatically with corresponding time sequences.

Statistics
The data were analyzed using the statistical package SPSS 16.0 for Windows (SPSS Inc). Parametric tests were used throughout, be-
cause data were sufficiently normally distributed initially or after log-normal transformation. Stress responses were expressed in 2 different ways, as absolute responses (mean values during stress) and as Δ responses (absolute responses with subtracted baseline levels). The paired-samples t test was used to assess whether the absolute response during stress was significantly different from baseline. Stress response stability over time was assessed by paired-samples t test and Pearson correlations. Data are presented as mean ± SD unless otherwise specified. A significance level of 5% was used throughout.

Results

Entry and follow-up characteristics of our study participants are presented in Table 1. During the 18-year observation period, established risk factors like BP, cholesterol, and body mass index increased significantly. Details of medications and medical conditions at follow-up have been described previously.9

Responses to Stress Tests

The CV and catecholamine responses to CPT and MST on the 2 occasions are illustrated in Figure 1. All of the CV and sympathoadrenal variables during MST and CPT on both occasions increased significantly from baseline, except for heart rate and epinephrine responses to CPT at follow-up. The Δ responses differed significantly on the 2 occasions for all of the CV variables, except for diastolic BP during CPT. Furthermore, Δ responses were somewhat lower at follow-up for all of these variables, except for the systolic BP response to the CPT, which was slightly higher at follow-up, and diastolic BP response to CPT that was similar on the 2 occasions.

Correlations Between Initial and Follow-Up Stress Responses

Table 2 summarizes 18-year follow-up correlations of baseline and absolute and Δ responses with respect to BP, heart rate, and catecholamine parameters during the stress tests. All of the correlations of CV variables were significantly different from 0. The correlation coefficients were, in general,
Table 2. Eighteen-Year Entry/Follow-Up Correlations of Cardiovascular and Catecholamine Parameters During the MST and the CPT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MST</th>
<th></th>
<th>P</th>
<th>MST</th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>r</td>
<td></td>
<td>n</td>
<td>r</td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>76</td>
<td>0.39</td>
<td>†</td>
<td>76</td>
<td>0.42</td>
<td>†</td>
</tr>
<tr>
<td>Diastolic BP</td>
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<td>0.45</td>
<td>†</td>
<td>77</td>
<td>0.30</td>
<td>†</td>
</tr>
<tr>
<td>Heart rate</td>
<td>76</td>
<td>0.50</td>
<td>†</td>
<td>77</td>
<td>0.53</td>
<td>†</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>74</td>
<td>0.30</td>
<td>†</td>
<td>77</td>
<td>0.26</td>
<td>*</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>74</td>
<td>0.24</td>
<td>*</td>
<td>76</td>
<td>0.16</td>
<td>NS</td>
</tr>
<tr>
<td>Stress (absolute)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
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<td>0.79</td>
<td>†</td>
<td>73</td>
<td>0.49</td>
<td>†</td>
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<tr>
<td>Diastolic BP</td>
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<td>73</td>
<td>0.55</td>
<td>†</td>
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<tr>
<td>Heart rate</td>
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<td>†</td>
<td>74</td>
<td>0.56</td>
<td>†</td>
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<tr>
<td>Epinephrine</td>
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<td>0.62</td>
<td>†</td>
<td>71</td>
<td>0.38</td>
<td>†</td>
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<tr>
<td>Norepinephrine</td>
<td>65</td>
<td>0.29</td>
<td>*</td>
<td>71</td>
<td>0.18</td>
<td>NS</td>
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<tr>
<td>Stress (Δ)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>73</td>
<td>0.65</td>
<td>†</td>
<td>73</td>
<td>0.25</td>
<td>*</td>
</tr>
<tr>
<td>Diastolic BP</td>
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<td>0.66</td>
<td>†</td>
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<td>†</td>
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<tr>
<td>Heart rate</td>
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<td>†</td>
<td>74</td>
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<td>†</td>
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<td>0.50</td>
<td>†</td>
<td>71</td>
<td>0.36</td>
<td>NS</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>63</td>
<td>0.25</td>
<td>*</td>
<td>70</td>
<td>0.53</td>
<td>NS</td>
</tr>
</tbody>
</table>

Baseline is after 30 minutes of supine rest; stress (absolute), absolute response during stress; stress (Δ), absolute response during stress subtracted baseline. NS indicates not significant.

The significance level of the Person correlations (r) is labeled, with *P<0.05, †P<0.01, ‡P<0.001, or NS.

higher for the MST responses than the CPT responses, regardless of whether Δ values or absolute values during stress were analyzed. However, the correlation coefficient for SBP during MST (95% CI: 0.69 to 0.86) was the only variable that was significantly higher than during CPT (95% CI: 0.30 to 0.65). Regarding catecholamine reactivity, epinephrine concentration during mental stress also showed a high correlation (r=0.62; P<0.001; 95% CI: 0.45 to 0.75) compared with epinephrine concentration during CPT (r=0.36; P=0.003; 95% CI: 0.10 to 0.52). Moreover, absolute response correlations tended to be higher than Δ response correlations. The correlations at baseline and at the 18-year follow-up of systolic BP and epinephrine concentration during the MST are illustrated in Figure 2.

Participants from the highest screening percentile during the selection process had, in general, higher absolute responses during stress than participants from the lower screening percentiles, particularly concerning systolic BP, heart rate, and epinephrine responses to mental stress. However, separate analyses within the different selection groups tended to show significant 18-year Pearson correlations during the MST, that is, systolic BP during MST, for group 1 (r=0.64; P=0.001), group 2 (r=0.72; P<0.001), and group 3 (r=0.66; P<0.001).

Discussion

This is the first study to show long-term test-retest correlations of both CV and catecholamine responses to laboratory stress. CV absolute responses reached significant 18-year correlations of 0.5 to 0.8 both to CPT and MST. The correlation of systolic BP during MST was significantly higher than during CPT, and there was a tendency that correlations of MST responses were higher than correlations of CPT responses. Moreover, plasma epinephrine responses during the MST reached an r value of 0.6. Our findings indicate high long-term stability of sympathoadrenergic and CV responses to stress.

The selection procedure, per se, is not likely to cause a significant overestimation of our correlations. Our participants were initially selected from the low, middle, and high ranges of 1 single BP measurement during a military enlistment. Their screening BP probably consisted of 2 components, their true resting BP and a stress component attributed to the unusual circumstances of the enlistment procedure, making the BP measurement more similar to absolute values during mental stress. Some might argue that, because these 3 selection groups consist of participants with different resting BP, they may also possess different characteristics that may enhance the degree of correlation. However, when resting BP was repeated in the laboratory during the first examination, BP differences between the selection groups were reduced and systolic BPs assumed normal distribution, thus indicating a typical regression to the mean phenomenon. In our material there is indeed a tendency that participants from higher screening percentiles demonstrated higher mean responses. These differences could potentially contribute to strong correlations. However, the variables showing the most prominent mean differences during the MST also tended to show significant 18-year Spearman correlations within the different selection groups. This indicates that stability of stress responses is a general characteristic regardless of which initial percentile the subjects belonged to.

The BP measurements were recorded differently on the 2 occasions. Intra-arterial measurement on the first occasion was replaced by a Finapres noninvasive beat-to-beat BP recorder on the second occasion. Absolute values of noninvasive measurements are slightly different from intra-arterial measurements. However, by using continuous measurements of BP, the possibility that the measurement procedure itself affected the BP recording was minimized. Previous studies have shown that several measurements during stress tests increase reproducibility. By using sequences of several measurements, the accuracy was probably increased in our study.
Another limitation of the present study is the use of venous as opposed to arterial catecholamines at follow-up. The change of methods provides less information about the stability of catecholamines and the sympathetic system. Epinephrine is secreted from the adrenal gland, and the arterial concentration is higher than venous.\(^{15}\) Resting plasma epinephrine concentration tends to decrease throughout life, whereas resting plasma norepinephrine increases significantly with age.\(^{16}\) The main source of plasma norepinephrine is spillover from sympathetic nerve terminals. There is a considerable uptake and release of norepinephrine in all tissues, and under normal circumstances there are no significant arterial and venous differences in plasma norepinephrine in the forearm. However, norepinephrine from the antecubital vein overrepresents the sympathetic activity to the forearm compared with other tissues. Moreover, there is not necessarily a linear association between arterial and venous concentration during MST and CPT; thus, arterial and venous catecholamines may be related to different physiological mechanisms on the 2 occasions. All of these considerations make the interpretation of the catecholamine responses difficult. Several samples during the stress tests probably improved the accuracy. However, the methodological limitations mentioned are more likely to underestimate than overestimate our correlations.

MST and CPT are considered to activate the sympathetic system differently.\(^{17}\) The response to MST is mainly caused by central activation with a subsequent stimulation of \(\beta\)-adrenergic receptors. The CPT is mainly thought to stimulate peripheral afferent activity, and the vasoconstrictor effect is largely because of stimulation of \(\alpha\)-adrenoceptors.\(^{6}\) The magnitude of heart rate and epinephrine responses to MST appears larger than responses to CPT on both occasions, consistent with the theory outlined. Moreover, the responses to MST seemed to be more stable than the responses to CPT. The correlation coefficient of systolic BP (absolute response) was significantly higher during MST than during CPT. There was a clear tendency of higher correlation coefficients when comparing MST responses with CPT responses. A few methodological and statistical factors that could possibly contribute to these differences should be discussed. CPT lasted only for 1 minute as opposed to 5 minutes of MST. During the CPT there was generally a rise in all of the variables through the whole minute, and it is possible that not all of the participants reached their hypothetical peak response. Values calculated during the MST perhaps better reflect the true mean response during stress. In addition, stress variables during CPT consisted of 2 measurements compared with 3 measurements during MST. Concerning the CPT, catecholamine samples were collected at 30 and 60 seconds on the first occasion versus 1 sample at the second examination. During the MST, on the other hand, 3 samples were obtained on both occasions. Fewer recordings may reduce the relative accuracy of the CPT measurements and thereby possibly reduce the level of correlations. The variability of responses to the MST was greater than to the CPT, indicated by higher SDs, theoretically influencing the level of correlation. We do not know whether any of the aspects mentioned actually have affected the results. Overall, however, we do not think that the methodological considerations above can explain all of the differences in correlations between the CPT and the MST. The general tendency was consistent for all of the variables, although BP and catecholamines were assessed differently. Moreover, the differences were consistent when on the basis of both absolute responses and \(\Delta\) responses. Because \(\beta\)-receptors are supposed to become downregulated with increasing age, unlike \(\alpha\)-receptors, Sherwood et al\(^{6}\) have suggested that the \(\alpha\)-mediated response to CPT would probably be more stable in the long term. However, our results may indicate that the \(\beta\)-mediated response to MST is more stable.

Our major finding was a high stability in stress responses during this 18-year follow-up period. A previous meta-analysis found that reproducibility of heart rate and BP to laboratory stress was moderate (\(r=0.35\) to 0.56), although the test-retest intervals were relatively short.\(^{4}\) On the basis of this report, it was anticipated that our results would provide lower correlations than those reported previously in test-retest studies of shorter duration. However, our test-retest correlations turned out to be better.

A 10-year follow-up study presented correlations to a mentally challenging aversive reaction time task of \(\Delta\) systolic BP (\(r=0.46\)), \(\Delta\) diastolic BP (\(r=0.20\)), and \(\Delta\) heart rate (\(r=0.37\)). In our study, all of the correlations during the MST were higher.\(^{6}\) The previous study also presented correlations of \(\Delta\) responses to a CPT. These findings were similar to ours. Correlations of absolute responses were, unfortunately, not presented in their study.

A study assessing 1-year stability of catecholamines and CV variables provided stress level correlations of epinephrine (\(r=0.55\)), norepinephrine (\(r=0.70\)), systolic BP (\(r=0.41\)), diastolic BP (\(r=0.41\)), and heart rate (\(r=0.81\)) during a calculation task comparable with our MST.\(^{7}\) The numeric correlations of systolic and diastolic BPs were considerably higher in our study, whereas this was not the case regarding heart rate and norepinephrine.

Concerning epinephrine, we found that intra-individual variation during a single stress session was substantially higher compared with the variation of CV stress variables. This may be attributable to the complex measurement technique, the pulsatile fashion of epinephrine secretion, and the short half-lives.\(^{7}\) In light of this, combined with the fact that the blood samples were of different origin, we found a high 18-year correlation of adrenaline during MST, with a correlation being on the same level as stated in the previous 1-year follow-up study.

The same study found that correlations between absolute responses during stress were twice as high as \(\Delta\) responses.\(^{7}\) Burleson et al\(^{7}\) list 7 studies in which stress values were more reproducible than \(\Delta\) values. Although correlations on the basis of absolute responses were not significantly higher than correlations on the basis of \(\Delta\) responses in our study, the numeric correlations were consistently higher. In a meta-analysis, articles that did not provide \(\Delta\) scores were excluded.\(^{5}\) Delta values have often been the preferred variable of interest to separate the predictive effect of resting BP from the stress response, per se. By calculating \(\Delta\) values, the resting BP component is seemingly removed, and the new variable only reflects the additional response provoked by the stress test. This assumption might, however, be oversimplified. The main explanation of the infe-
iority of Δ values has so far been confined to measurement error considerations. The uncertainty of Δ values may be larger because it is based on 2 separate measurements.

A different and crucial aspect concerning the validity of Δ values is whether the measurements during rest truly reflect the resting state. Although several attempts have been made in the protocol to facilitate a true baseline value, it is possible that the baseline value also include a stress component because of the laboratory environment. This component can be even more expressed in hyperreactive subjects, potentially labeling these individuals as normoreactors and, thus, underestimating the predictive effect of Δ responses to stress. Interestingly, a previous report on the basis of the same material as that presented in this article found that systolic BP, epinephrine, and norepinephrine responses to MST substantially increased the possibility to predict resting BP 18 years later. Moreover, absolute responses at the initial examination increased the prediction of BP more than Δ responses. This indicates that absolute responses during stress may be superior to Δ responses when assessing stress reactivity.

We have used correlation analysis to describe stability. However, correlations can only indicate whether individuals that respond in the low or high range continue to respond in a low or high range, and it does not provide information about the stability of the response magnitude. Generally, the response magnitudes were quite similar on the 2 occasions in our study. Regarding the CV variables, the mean responses were generally slightly attenuated at the second examination. Functional and structural changes associated with aging may partly be responsible for this. Neither epinephrine nor heart rate responses were significant at the follow-up CPT, and the Δ responses were clearly attenuated compared with the initial reactions, suggesting that the physiological responses to the CPT may have changed during the 18-year period. The reduced heart rate response may be related to the concomitant lack of increase in epinephrine; however, because the concentration of catecholamines differs in arterial versus venous blood, these results must be interpreted with caution. The lower epinephrine concentration at follow-up was most likely attributable to venous instead of arterial sampling. In addition, aging may also reduce epinephrine levels. The increase in norepinephrine concentration at follow-up was substantial and is consistent with the gradual increase in norepinephrine concentrations observed during aging. Norepinephrine responses had consistently lower levels of correlation than epinephrine, which may be explained by the more complicated mechanisms underlying plasma norepinephrine and possibly significant arterial and venous differences.

With the limited number of participants in most of these test-retest studies, the CIs for the correlations are wide, and, consequently, hardly any correlations can be claimed to be significantly higher or lower than others. However, our 18-year correlations are on the same level as those reported in previous studies of much shorter test-retest intervals. Our study, therefore, supports the notion that CV and epinephrine responses, particularly to mental stress, constitute relatively stable individual characteristics that, only to a modest extent, change as years go by.

Perspectives

There are many aspects that challenge the reactivity hypothesis. Previous findings of stress responses with low-to-moderate stability on the basis of relatively short follow-up intervals have been one major objection. Our results, however, indicate that concerns about long-term stability should be less of an issue when considering the importance of hyperreactivity in the development of HT and CVD.

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Disclosures

None.

References

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