FREQUENTLY ASKED QUESTIONS

Please contact us if you have a question you would like answered that does not appear below.

Q1. What does VENDYS® measure?

A1. In simple terms, VENDYS® measures vascular reactivity.

Q2. What is "vascular reactivity"?

A2. Vascular reactivity is a vital component of vascular function that enables the circulatory system to respond to physiologic and pharmacologic stimuli that require adjustments of blood flow and alterations of vessel tone and diameter. Vascular reactivity occurs in two forms – vasoconstrictive and vasodilative – and can be exhibited at both the macrovascular and microvascular levels.

Q3. What is the definition of "macrovascular" and "microvascular"?

A3. "Macrovascular" pertains to large, conduit arteries with an internal diameter greater than 100 microns. "Microvascular" refers to small, resistance vessels (pre-capillary arterioles) with an internal diameter of less than 100 microns. It is estimated that the microvasculature accounts for over 95% of the total body vasculature.

Q4. What is the relationship between "vascular reactivity" and "endothelial function"?

A4. Microvascular reactivity (here,vasodilative reactivity) causes reactive hyperemia (increased blood flow in response to ischemia or similar pharmacologic stimuli), whereas macrovascular reactivity (flow mediated dilatation, or FMD) results from reactive hyperemia. Both macro- and microvascular reactivity are governed by multiple physiologic (endothelium-dependent and –independent) regulatory mechanisms and are mediated by a number of biochemical agents, such as nitric oxide (NO), prostaglandins, adenosine, bradykinin, histamine, and other vasoactive substances. It is believed that macrovascular reactivity is predominantly mediated by endothelium-derived NO, whereas microvascular reactivity is only partially mediated by NO. Traditionally, assessment of macrovascular reactivity (FMD) at the brachial artery level by high resolution ultrasound imaging has been described as an endothelial function test. However, some key opinion leaders believe that "endothelial function" is a misnomer because endothelial cells have numerous functions. Moreover, endothelial cells exist in all vascular beds and play critical roles at both macro- and microvascular levels.

Q5. How does VENDYS® measure vascular reactivity?

A5. VENDYS® monitors, records, and analyzes fingertip temperature, which serves as a surrogate marker of blood flow changes that result from vascular reactivity. The VENDYS® test begins with an automated blood pressure measurement in the left arm, followed by a period of suprasystolic cuff occlusion of the right arm (usually 5 minutes). During the cuff occlusion, fingertip temperature in the right hand falls because of the absence of warm circulating blood. The occlusion of blood flow elicits a vasodilatory response in the ischemic area. Once the cuff is released, blood flow rushes into the forearm and hand, causing a temperature rebound (TR) in the fingertip which is directly proportional to the reactive hyperemia response. The higher the temperature rebound, the better the vascular reactivity.

Q6. Does VENDYS® temperature rebound (TR) change in the presence of nitric oxide (NO) inhibitors?

A6. Studies have shown that cutaneous microvascular reactivity, measured by laser Doppler flowmetry (LDF, the current, standard method of measuring skin blood flow), is blunted by NO synthase inhibitors. Similar studies using VENDYS® are underway. These studies not only investigate the effect of an eNOS (endothelial NO synthase) inhibitor on fingertip temperature reactivity in the occluded arm, but also aim to test the hypothesis that increased temperature in the contralateral finger during cuff occlusion is partly effected by eNOS and nNOS (neuronal NO synthase).

Q7. How does the VENDYS® method compare to laser Doppler flowmetry (LDF)?

A7. Several studies have shown that skin temperature correlates strongly with skin blood flow measured by LDF. However, unlike LDF, which is sensitive to red blood cell motion only at the skin level (1-2 mm depth), VENDYS® temperature signals can reflect blood flow changes in both skin and subcutaneous tissues simply because the heat from the inrush of warm blood travels from deep tissues to the skin surface. Also, LDF is markedly sensitive to any movement at the measurement site, whereas VENDYS® is not affected by finger motion.

Q8. How does the VENDYS® method compare to Doppler ultrasound flow velocity measurement?

A8. Our studies have demonstrated a direct relationship between VENDYS® parameters and flow velocity changes in the radial and ulnar arteries at the wrist level. In most circumstances, fingertip temperature changes appeared to reflect changes in Doppler blood flow velocities, but with dampened amplitudes as well as lower noise. Unlike Doppler ultrasound, which is reliant on proper probe placement and handling by the operator, VENDYS® temperature recording is automated and does not require probe handling. Our studies have also shown a disparity between Doppler velocity measurements and VENDYS® parameters when the fingertip temperature approaches (>35°C) body core temperature (37°C).

Q9. What is the correlation between VENDYS® and other vascular function tests?

A9. VENDYS® has been studied in relation to FMD-BAUS (flow mediated dilatation-brachial artery ultrasound), Doppler flow velocity, LDF (laser Doppler flowmetry), and PAT (peripheral arterial tonometry-EndoPAT). In summary, VENDYS® exhibited modest correlations with these methods. We believe that VENDYS®, by reflecting both cutaneous and deep tissue vascular reactivity, introduces a new angle to vascular function assessment and does not equate with any of the above techniques; in fact, based on our preliminary studies, VENDYS® is a very sensitive marker of vascular (and neurovascular) reactivity and may prove to be the most useful and cost effective clinical tool for monitoring vascular function.

Q10. How does the VENDYS® method compare to EndoPAT® peripheral artery tonometry?

A10. Although both EndoPAT® and VENDYS® measure vascular reactivity at the fingertip and employ a similar cuff-induced reactive hyperemia procedure, the EndoPAT® probe includes a fingertip cuff that obstructs microvasculature at the point of measurement; therefore, EndoPAT® may not be able to accurately evaluate microvascular reactivity at the fingertip. Studies have shown a modest correlation ($r=0.29$, $p=0.01$) between EndoPAT® reactive hyperemia index (RHI) and VENDYS® temperature rebound (TR).

Q11. How well does VENDYS® correlate with conventional cardiovascular risk factors (Framingham Risk Score), subclinical atherosclerosis (coronary calcium score), and obstructive coronary artery disease (coronary angiography and myocardial perfusion)?

A11. Our studies have clearly demonstrated that lower VENDYS® fingertip temperature rebound (TR) is associated with increased Framingham Risk Score (FRS) and higher coronary calcium score (CAC). More importantly, TR has been shown to significantly improve the predictive value of FRS in the detection of high-risk, subclinical atherosclerosis (CAC>100) in asymptomatic population. Similarly, we have also found that a combination of TR and FRS has shown a higher predictive power in the identification of obstructive coronary artery disease (diagnosed by coronary angiography and myocardial perfusion imaging) in vaguely symptomatic patients. These data suggest a potential clinical utility for VENDYS® as a complementary, non-invasive, non-imaging, inexpensive test for cardiovascular risk assessment in asymptomatic and vaguely symptomatic populations. For more information, please see the Clinical Findings Section.

Q12. How reproducible are VENDYS® results? (Intra-individual and inter-observer variability)

A12. Our intra-individual repeatability studies (24-hour interval) in apparently healthy individuals have shown that VENDYS® parameters, TR (temperature rebound) and AUC (Area Under Curve), are reproducible when performed under the recommended standard test conditions (see below). The coefficient of variation (CV) was 5.7% for temperature rebound (TR), 8.7% for mean arterial pressure

(MAP), and 11.4% for heart rate (HR). These data indicate that TR reproducibility fits within the accepted reproducibility range for methods that have been widely adopted in clinical practice, namely MAP and HR.

> It is important to realize that VENDYS®, like other cardiovascular physiologic markers (e.g., blood pressure and heart rate), is sensitive to factors such as autonomic nervous system activity and postprandial metabolic changes. Therefore, for maximum reproducibility, VENDYS® tests should be performed under optimum conditions with minimum disturbing factors that would influence the cardiovascular system. Recommended subject and testing conditions are listed in the International Brachial Artery Reactivity Task Force guidelines (J Am Coll Cardiol 2002 Jan;39(2):257-65.) and in the VENDYS® Operating Manual.

The VENDYS® testing procedure (temperature measurement, thermal analysis, report generation) is completely automated. Therefore, inter-observer variability is not an issue.

Q13. What is "hot finger", and how does diurnal variation in fingertip temperature affect VENDYS® test results?

A13. Studies have shown that resting fingertip temperature usually ranges from 27°C to 33°C (average 30°C) and is primarily affected by mental stress, physical activity, and thermoregulatory mechanisms (in response to ambient temperature and metabolic activity). It is well known that fingertip temperature varies with the status of autonomic nervous system activity in such a way that the higher the sympathetic activity, the lower the fingertip temperature. Also, temperature rebound (TR) appears to be inversely correlated with the starting fingertip temperature. As the starting temperature increases above 33°C (and approaches core body temperature, 37°C), the magnitude of temperature rebound appears to be artificially reduced in such a way that the higher the starting temperature, the lower the TR (possibly resulting in a negative TR). This effect occurs because maximum fingertip temperature usually does not exceed core body temperature. To address this issue, Advanced VENDYS® Analysis Software provides normalized TR and other VENDYS® indices, such as area under the curve (AUC), slope of temperature recovery (SLP), and bioheat vascular reactivity index. However, in our initial clinical studies, we chose TR because it was the simplest index of thermal reactivity. Despite the apparent "dampening effect" of high starting temperatures on temperature rebound, unadjusted TR has demonstrated strong predictive value in multiple clinical studies, as shown in the Clinical Findings section. (See VENDYS® Operating Manual for additional information.)

Q14. What is "cold finger", and what should be done about it?

A14. We define "cold finger" as a baseline fingertip temperature below 27°C. This situation is usually indicative of heightened, sympathetic nervous system activity (from mental stress, anxiety, pain, etc.), although it may also result from vasospasm (e.g., Raynaud's phenomenon) or cold ambient temperature. As stated in the International Brachial Artery Reactivity Task Force guidelines, these situations are sub-optimal for vascular function measurement and must be addressed by reducing mental stress, warming the subject's hands (preferably with dry heat), and increasing the room temperature. If all attempts to relax the subject and increase the fingertip temperature fail, it is recommended that VENDYS® testing be rescheduled.

N.B. Despite the apparent noise effect of "cold finger" and fingertip vasoconstriction on temperature response curves, our preliminary investigations have suggested that sympathetic overactivity during performance of the VENDYS® test may be an indication of abnormal neurovascular response and signals a higher cardiovascular risk.

Q15. What are the recommended test conditions?

A15. The optimum conditions for VENDYS® testing are similar to optimum conditions for measuring blood pressure and other vascular function and reactivity tests. A comprehensive list of such conditions has been outlined by the International Brachial Artery Reactivity Task Force and is included in the VENDYS® Operating Manual.

Q16. How often can VENDYS® tests be performed?

A16. The answer is not quite clear. However, research studies have suggested that 5 minute cuff occlusion creates a "vascular memory" effect that may require 30 minutes, or more, to reset. Therefore, cuff reactive hyperemia studies, such as the VENDYS® test, should be performed at least 30 minutes apart.

Q17. What is the second temperature probe used for?

A17. The second probe monitors fingertip temperature changes on the contralateral, non-occluded hand. Temperature data from the second probe were originally intended to serve as a relatively stable, reference curve. However, recent studies have revealed that temperature changes in the non-occluded hand may provide additional insight into the subject's vascular function. It is hypothesized that increased fingertip temperature in the contralateral hand is a physiologic, neurally-mediated, systemic response to the ischemic stimulus. It is further hypothesized that this response would be vasodilatory in healthy individuals and hampered in individuals with cardiovascular risk factors and sympathetic overactivity. For more information, please see "Page 25 – Latest Findings."

Q18. How long is cuff occlusion?

A18. Traditionally, reactive hyperemia tests have been performed using a 5-minute protocol because flow-mediated dilatation of the brachial artery has been found to plateau after 5 minutes cuff occlusion. However, our preliminary studies have shown that fingertip temperature rebound after a shorter period of cuff occlusion (as short as 2 minutes) can distinguish individuals with increased cardiovascular risk (higher Framingham Risk Score, higher coronary calcium score, abnormal myocardial perfusion, and obstructive coronary artery disease). Note that observed temperature rebound values will be higher with 2 minute cuff occlusion than with 5 minute occlusion, simply because the fingertip temperature will fall further during a longer period of cuff occlusion. It is recommended that VENDYS® users choose and utilize a consistent duration of cuff occlusion if they wish to compare TR values.

Q19. Does 5-minute cuff occlusion pose any risk to the subject?

A19. Numerous studies have used 5-minute cuff occlusion and reported no significant problems. However, it is recommended that VENDYS® testing be aborted if the subject complains of excessive pain or discomfort. In our studies involving over 1500 subjects, only one subject experienced this problem. In some subjects, mild skin bruising occurs at the cuff site.

Q20. In what format are VENDYS® data files stored? Can the data be exported to data analysis software?

A20. In addition to showing a real-time, graphical display and saving the test results in the VENDYS® database (SQL), the raw data can be exported in .CSV and .XML formats to other databases.

Q21. How long does the VENDYS® test take to complete?

A21. The entire test procedure can usually be completed in 15 minutes. Details are provided in the VENDYS® Operating Manual.

Q22. What does Advanced VENDYS® Analysis Software provide?

A22. The software performs an extensive analysis of temperature data obtained from both fingers and generates a detailed report of multiple parameters, including temperature rebound (TR), area under the curve (AUC), slope of temperature fall and recovery, and parameters obtained using advanced bioheat algorithms. Also included are adjusted values for TR and AUC, based on various starting fingertip temperatures.

Q23. What is adjusted Temperature Rebound (aTR), and what is the unit of measurement, °Celsius or °Fahrenheit?

A23. The VENDYS® software utilizes a proprietary method to calculate what the fingertip temperature rebound curve would look like if no vascular reactivity were present, taking into account the starting fingertip temperature and the amount of temperature fall during cuff occlusion. The difference between this "zero reactivity curve" and the actual observed temperature curve is used to determine the *adjusted* temperature rebound (aTR) presented in the VENDYS® test report. Consequently, aTR is a dimensionless number whose magnitude directly correlates with the extent of the subject's vascular reactivity. The higher the aTR, the higher the vascular reactivity, the better the vascular function…

Q24. What are suggested topics for future VENDYS® research studies?

A24. We encourage our colleagues to investigate the following:

- Correlation between changes in VENDYS® and carotid IMT, in response to therapy
- Changes in VENDYS® during treatment with low versus high dose statins
- Changes in VENDYS® during treatment with anti-hypertensive medications
- Relationship between VENDYS® and inflammatory biomarkers (hsCRP, Lp-PLA2, IL-6, …)
- Correlation between VENDYS® and coronary flow reserve and vasoreactivity
- Correlation between VENDYS® and plaque characterization by VH-IVUS
- VENDYS® for prediction of the development of hypertension in at-risk individuals
- VENDYS® for monitoring response to treatments in patients with chronic heart failure
- VENDYS® for prediction of the development of pre-eclampsia
- VENDYS® for early detection of vascular dysfunction associated with erectile dysfunction
- VENDYS® for early detection of vascular dysfunction associated with peripheral arterial disease
- VENDYS® for the combined, ambulatory monitoring of vascular function and blood pressure
- Effects of various inhibitors of nitric oxide synthase on VENDYS® indices of vascular and neurovascular reactivity

- VENDYS® for monitoring response to non-pharmacologic therapies (diet, exercise, smoking cessation, stress reduction, etc.)
- VENDYS® for preoperative risk stratification and prediction of morbidity and mortality
- Acute and chronic effects of psychological stress on VENDYS®
- Comparison of VENDYS® markers of vascular and neurovascular reactivity in 2- versus 5- versus 10-minute cuff occlusion protocols
- Comparison of predictive value of VENDYS® testing of the lower extremities (utilizing cuff occlusion at the thigh or calf level and VENDYS® probe placement on the toe) with typical testing of the upper extremities; comparison of toe/finger reactivity versus the traditional ankle/brachial index

Other important topics are welcomed. Endothelix® provides special offers to investigators whose areas of research overlap with any the topics listed above.