Clinical approach to cardiovascular reflex testing

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Introduction
The evaluation of impairment of cardiovascular control comprises a prelaboratory and a laboratory phase. The prelaboratory evaluation, in the office or at the bedside, consists of a medical history, physical and neurologic examination and routine blood and urine testing. The prelaboratory phase is indispensable for a differentiation between impairment of cardiovascular control per se and a non-cardiovascular disorder presenting with or mimicking cardiovascular dysfunction. Examples of the latter group are neurologic disorders (seizures, migraines, vertebrobasilar transient ischemic attacks), vertigo (in particular benign positional vertigo), psychiatric disorders (generalized anxiety disorder, panic disorder). The laboratory evaluation of cardiovascular dysfunction serves as an extension of the clinical evaluation. Indications for testing of cardiovascular reflexes in our laboratory include suspicion of physiologically significant autonomic failure, assessment of syncope and evaluation of the effectiveness of management of orthostatic disorders.

Measurement of blood pressure in supine and standing position with a sphygmomanometer and stethoscope is sufficient for an initial evaluation of patients suspected to suffer from marked disturbances in cardiovascular control. However, less overt forms of cardiovascular dysfunction are not easily detected by this method. In recent years the measurement of continuous noninvasive blood pressure has become available [1]. The Finapres device tracks changes in blood pressure from the finger artery in close agreement with intra-brachial and intra-radial arterial blood pressure recordings. From the arterial pulse waves beat-to-beat values of stroke volume and systemic vascular resistance can be computed since pulse contour algorithms [2] and the Modelflow simulation of the arterial system have been developed [3]. More recently, on-line examination of blood pressure and hemodynamic parameters has become available by dedicated software programs (BM1-Modelflow, TNO-BM1, Amsterdam, The Netherlands). These developments enable the physician to relate disabling cardiovascular symptoms in a patient to changes in blood pressure and the underlying hemodynamic disturbances. This facilitates a more precise diagnosis in an individual patient.

This paper is concerned with the clinical assessment of baroreflex mediated cardiovascular control and the use of continuous blood pressure recording. The first section deals with the control of systemic blood pressure by the arterial baroreflex. The second section is concerned with the evaluation of patients with syncope. In the third section the application of continuous blood pressure monitoring in the management of patients with orthostatic intolerance is discussed.

Clinical assessment of baroreflex control of arterial blood pressure
For the purposes of the following discussion we have simplified neural cardiovascular control by assuming that the arterial baroreceptor reflex is solely responsible for short term circulatory homeostasis.

The arterial baroreflex pathways can be divided in an afferent and an efferent limb, both containing peripheral and central structures. The afferent limb comprises the baroreceptors located in the carotid sinus and aortic arch, their afferent nerve fibers, the nucleus tractus solitarius and a complex wiring system ending in the nucleus ambiguus and the rostroventrolateral medulla. The pathways running from the latter brain stem structures to the heart and blood vessels will be regarded as the efferent limb.

The arterial baroreflex acts as a negative feedback system with the carotid sinus and aortic arch blood pressure as input signal and heart rate, cardiac contractility, venous capacitance and systemic vascular resistance as controlled variables. To counterregulate a blood pressure reduction heart rate and cardiac contractility are increased and vasoconstrictor tone augmented. The change in heart rate can be established within one heart beat by influencing the parasympathetic outflow from the area of the nucleus ambiguus to the sinoatrial node of the heart. The most effective action of the baroreflex to counterregulate a blood pressure reduction is the withdrawal of its inhibitory activity on the rostroventrolateral medulla. This produces an increase in neural sympathetic vasomotor outflow which is followed by vasoconstriction of the resistance and capacitance vessels.

Cardiovascular reflex tests evaluate arterial baroreflex pathways by blood pressure and heart rate responses to a variety of physiological stresses (Table 1). It must be emphasized that both the autonomic nerves, end-organ responsiveness and circulatory hemodynamics are involved and that only indirect information about a complex cardiovascular reflex loop is obtained.

The circulatory response to active standing is central in our assessment of the baroreceptor reflex integrity in an individual patient. First, active standing represents a real life condition and is clinically relevant. It evokes recognizable symptoms in patients suffering from orthostatic intolerance. Second, the physiology of orthostatic stress testing has been studied in detail and a spectrum of normal and abnormal circulatory responses can be defined. Third, the manoeuvre can be applied both in young and older subjects and interpreted since age related reference values are available. Finally, confounding

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**Table 1. Non-invasive cardiovascular reflex tests.**

<table>
<thead>
<tr>
<th>Cardiovascular innervation tests</th>
<th>Overall</th>
<th>Initial response upon standing</th>
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<td>Valsalva's manoeuvre</td>
<td>Overall</td>
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<td>Cold face test</td>
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<tr>
<th>Vasomotor innervation tests</th>
<th>Overall</th>
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<td>Valsalva's manoeuvre</td>
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<td>Cold pressor test</td>
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Abbreviations used: Finap, finger arterial blood pressure; HR, heart rate; CO, cardiac output; SVR, systemic vascular resistance.
variables are well known and the within-repeatability of
the test is excellent [4].

For long-duration orthostatic stress testing (20-45 min
upright) we prefer head-up tilting. It gives better
experimental control, minimizes skeletal muscle
contractions and muscle fatigue and allows rapid return to
the supine posture in case of impending syncope in the
head-up posture. In clinical practice we also use head-up
tilt testing in patients with motor impairment and a
disability to stand actively.

Valsalva’s manoeuvre is another test that can be applied
to assess overall baroreceptor reflex arc function. Its
advantage is that both the capacity for cardio-acceleration
and -deceleration are tested, but it only assesses
instantaneous circulatory responses. Lack of reference
values for blood pressure indices of Valsalva’s manoeuvre
and problems with applicability in very young and elderly
subjects make this procedure less suitable for the
assessment of cardiovascular control than orthostatic
stress testing.

When failure of the overall arterial baroreceptor reflex
has been established by an active standing test or
Valsalva’s manoeuvre, evidence whether the lesion is on
the afferent or on the efferent limb is obtained from
additional testing. The integrity of the efferent sympathetic
and/or parasympathetic pathways can be assessed by
evaluation of heart rate or blood pressure responses upon
stimulation of these pathways with afferent stimuli other
than blood pressure. Placing one hand in icewater, mental
stress and isometric exercise such as sustained handgrip
have been applied to assess efferent sympathetic outflow.
The afferent pathways involved are cold afferents and pain
afferents, central command and muscle receptor afferents.
These stimuli evoke similar absolute increases in
sympathetic neural activity and arterial pressure in
healthy young and elderly subjects [5]. In subjects with
evidence of disturbances in control of systemic blood
pressure during orthostatic stress or Valsalva straining, a
rise in blood pressure in response to these stresses
suggests that efferent sympathetic pathways are
functioning. In our experience placing one hand in icewater
is the most useful physiological stressor to test the function
of efferent sympathetic pathways.

Selective evaluation of efferent cardiac vagal pathways
can be performed by apnoeic face immersion (diving reflex),
the cold face test, eye-ball pressure (oculovagal reflex) or
the forced breathing manoeuvre. An instantaneous heart
rate decrease upon stimulation of vagal outflow in the first
three mentioned manoeuvres indicates intact efferent
cardiac vagal pathways, but the magnitude of the
responses can be quite small in normal subjects especially
at old age and, therefore, does not allow to distinguish
between normal and diminished efferent cardiac vagal
control. During the forced breathing manoeuvre both
cardiac vagal stimulation and inhibition are assessed.
There is general agreement that the magnitude of the
changes in heart rate (R-R interval) provides the best
estimate of efferent neural traffic of the vagus nerve to the
heart in humans, but the afferent pathways and central
mechanisms underlying the changes in heart rate to this
test are complex and the mechanisms involved remain
uncertain.

When abnormalities in the function of arterial baroreflex
pathways have been established, the integrity of the
afferent pathways from the arterial baroreceptor to the
medulla and further to the hypothalamus can be assessed
by the evaluation of venous plasma vasopressin
concentration upon hypotensive orthostatic stress [6]. The
evaluation of the venous plasma catecholamines in supine
and standing position and the evaluation of blood pressure
response upon intravenous bolus injection of phenylephrine
enables in most cases a distinction between preganglionic
and postganglionic sympathetic vasomotor failure. The
heart rate response to intravenous bolus injection with
atropine confirms the presence or absence of parasympathetic heart rate control [6].

Evaluation of cardiovagal function is commonly used to
document the presence and extent of autonomic
neuropathy in patients with peripheral nerve diseases. A
diminished heart rate responsiveness during forced
breathing has been shown to be an early sign of vagal
impairment which can be detected in the laboratory
setting. However, it is important to realize that it is not
impaired cardiovagal but abnormal vasomotor innervation
that underlies the vast majority of clinical problems in
patients with autonomic cardiovascular neuropathy. This
abnormality becomes usually manifest during orthostasis;
orthostatic dizziness and syncope are the main clinical
problems in these patients [7]. We will discuss them in
more detail in the next section.

Evaluation of patients with syncope.
In the clinic cardiovascular syncope can be differentiated
in syncope due to orthostatic hypotension, syncope due to
reflex mediated vasomotor instability (carotid sinus
syncope, situational syncope) and cardiac syncope. The
work up of suspected cardiac syncope will not be discussed
here.

Orthostatic intolerance
In our experience three main types of orthostatic
intolerance can be defined.

1) Initial orthostatic dizziness: Most people with intact
autonomic control have experienced a brief feeling of
dizziness 6 to 10 s after the onset of standing up rapidly,
especially after supine rest. Such "functional" spells of
dizziness are more common in the young and can be
attributed to an initial blood pressure fall upon standing.
After the initial fall a subsequent overshoot in pressure
with marked reciprocal heart rate changes are observed.
These changes are not present in the initial phase of a
passive change of posture on a tilt table (Fig. 1.) and have
been ascribed to the vasodilatory effects of muscle
contractions upon active standing [7]. We consider a fall of
more than 40 mm Hg in systolic pressure and/or more than
20 mm Hg in diastolic pressure in the initial phase as
abnormally large both in the young and in the elderly [4].

An extraordinarily large initial fall and sluggish recovery
in arterial pressure has been reported in healthy young
subjects with severe complaints of orthostatic dizziness
shortly after standing up. A reduced capacity to increase
sympathetic outflow is likely to underlie this functional
disorder [8,9], but the mechanisms remain to be
determined. In subjects with this disorder, orthostatic
intolerance presenting as postural tachycardia and
vasovagal fainting, are often present during prolonged
orthostatic stress (see below) [10]. A large initial blood
pressure fall and a sluggish recovery upon active standing
is also found in patients with surgical denervation of the
carotid baroreceptors (operation for carotid body tumors)
(Fig. 2). This abnormality is to be expected since the
carotid baroreceptors are of key importance for
adjustments to rapid changes in arterial pressure [4].

2) Progressive and persistent fall in blood pressure upon
standing: After 1-2 min upright we consider a persistent
fall in systolic pressure larger than 20 mm Hg and/or in diastolic
Heart Rate Variability

![Fig. 1. Hemodynamic changes upon active standing (left panel) and 70° head up tilting (right panel) in a 29-year old healthy young male. Blood pressure and heart rate are given in absolute values. Cardiac output and systemic vascular resistance were computed by the pulse contour method and presented in percentage change from supine control.](image1)

pressure larger than 5 mmHg abnormal both in the young and in the elderly [4].

In patients with efferent sympathetic vasomotor failure active standing is accompanied by a progressive and persistent fall of both systolic and diastolic blood pressure (Fig. 3). This is due to a diminished or even absent increase in systemic vascular resistance upon standing. The delayed and sluggish heart rate response often observed in these patients indicates that vagal heart rate control is completely disrupted. The heart rate increase in these patients represents the remaining sympathetic response. In patients with sympathetic vasomotor lesions and intact vagal heart rate control, an immediate large heart rate increase without relative bradycardia and consequently a persistent and marked heart-rate rise is observed. This response can be attributed to correct baroreceptor sensing of the marked progressive blood pressure drop [4].

3) Abnormal responses during sustained orthostatic stress: Disorders of orthostatic intolerance manifest themselves often during prolonged (5-10 min) and long duration (20-45 min) orthostatic stress. The most common manifestation is an excessive postural tachycardia. This condition is associated with mild autonomic neuropathy and vasomotor dysfunction has been suggested to underlie this abnormality [10]. The common faint is another event, which can be observed during sustained orthostatic stress. The actual faint is associated with systemic arteriolar vasodilation and cardiac vagal slowing and symptoms and signs of autonomic hyperactivity. Attenuated systemic vasoconstriction and exaggerated postural tachycardia are observed on approaching of the actual faint. Cardiac slowing occurs relatively late (Fig. 4) [11].

![Fig. 2. Hemodynamic changes upon active standing (left panel) and 70° head up tilting (right panel) in a 63-year old patient with baroreceptor denervation after operation for carotid body tumors. Abbreviations as in Fig. 1.](image2)

**Aging and orthostatic stress**

In the elderly arterial baroreflex mediated parasympathetic control of heart rate is consistently reduced. This physiological impairment appears to have little effect on arterial baroreflex control of blood pressure in normotensive healthy elderly. Systemic blood pressure is appropriately adjusted during acute and sustained orthostatic stress. It appears that neural outflow is adjusted as much as is required to obtain the appropriate level of systemic blood pressure, regardless of age [5]. The adjustment to orthostatic stress in healthy elderly appears, however, to be easily deranged if circulatory control is heavily taxed. This may occur during periods of hypovolemia or prolonged inactivity. Episodic hypotension during acute stress in physiological aging should be distinguished from conditions with chronic orthostatic hypotension due to autonomic failure and from reflex causes of hypotension.

**Syncope due to reflex mediated vasomotor instability.**

Monitoring of finger arterial pressure has been found useful for laboratory confirmation of the clinical diagnosis and in the management of reflex mediated syncope due to conditions like the carotid sinus syndrome and situational syncope (swallowing, coughing) [12]. Cardiovascular monitoring with Finapres can also be applied to evaluate situations that are less well known as a cause of (near)loss of consciousness [13].

Despite a thorough workup of patients with syncope in a large proportion of patients a definite cause of syncope is never established [12]. Preliminary data indicate that the standard cardiovascular reflex tests discussed above are of limited value at most to identify abnormal cardiovascular control in individual patients with recurrent unexplained syncope. Long-duration head-up tilting have been reported to be a promising provocative procedure in the evaluation
Heart Rate Variability

![Hemodynamic changes upon standing and head up tilting](image)

**Fig. 3.** Hemodynamic changes upon standing (left panel) and 70° head up tilting (right panel) in a 63-year-old patient with efferent baroreflex failure due to pure autonomic failure. Abbreviations as in Fig. 1.

and management of these patients. It has been argued that reproduction of symptomatic hypotension by this procedure can provide evidence implicating a neurally triggered bradycardia/hypotension syndrome as the underlying cause of the unpredictable episodes of syncope [12]. The diagnostic value of symptomatic hypotension induced by tilt table testing in a noninvasively instrumented elderly subject with unexplained syncope is probably considerably, but there are serious doubts about the utility of this procedure in evaluating syncope of unknown origin in young subjects. Susceptibility to vasovagal syncope is common in healthy children and teenagers without a history of postural complaints or frequent fainting and a positive tilt-table test, therefore, cannot be interpreted as solid proof of an innocent fainting response as the underlying cause of the syncope [11].

Continuous blood pressure monitoring and the management of patients with orthostatic intolerance. Physical counter manoeuvres like squatting and leg crossing are both convenient and effective for combating orthostatic diziness by increasing stroke volume [14,15]. We instruct our patients to use squatting as an "emergency" mechanism to rapidly increase venous return when presyncopal symptoms occur in the standing position. An advantage of leg-crossing is that this manoeuvre can be applied in daily life without bringing much attention to the patients problem. The increase in blood pressure induced by leg-crossing can immediately be demonstrated to a patient by showing the finger blood pressure tracing on a video screen. Patients can thereby practice to apply the manoeuvre effectively [16]. Measurement of finger arterial pressure can also be applied to evaluate the effectiveness of expansion of total body water on upright blood pressure in patients with orthostatic intolerance [17]. The ambulatory version of Finapres (Portapres) can be used to document the real effect of treatment on orthostatic hypotension in normal daily life and gives more insight in the benefit of treatment [18].

**References**


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