Obstructive Sleep Apnea

Patent Foramen Ovale Closure in Obstructive Sleep Apnea Improves Blood Pressure and Cardiovascular Function

Stefano F. Rimoldi,* Sebastian Ott,* Emrush Rexhaj, Stefano F. de Marchi, Yves Allemann, Matthias Gugger, Urs Scherrer, Christian Seiler

Abstract—Obstructive sleep apnea (OSA) is a frequent syndrome characterized by intermittent hypoxemia and increased prevalence of arterial hypertension and cardiovascular morbidity. In OSA, the presence of patent foramen ovale (PFO) is associated with increased number of apneas and more severe oxygen desaturation. We hypothesized that PFO closure improves sleep-disordered breathing and, in turn, has favorable effects on vascular function and arterial blood pressure. In 40 consecutive patients with newly diagnosed OSA, we searched for PFO. After initial cardiovascular assessment, the 14 patients with PFO underwent initial device closure and the 26 without PFO served as control group. Conventional treatment for OSA was postponed for 3 months in both groups, and polysomnographic and cardiovascular examinations were repeated at the end of the follow-up period. PFO closure significantly improved the apnea–hypopnea index (ΔAHI −7.9±10.4 versus +4.7±13.1 events/h, P=0.0009, PFO closure versus control), the oxygen desaturation index (ΔODI −7.6±16.6 versus +7.6±17.0 events/h, P=0.01), and the number of patients with severe OSA decreased significantly after PFO closure (79% versus 21%, P=0.007). The following cardiovascular parameters improved significantly in the PFO closure group, although remained unchanged in controls: brachial artery flow-mediated vasodilation, carotid artery stiffness, nocturnal systolic and diastolic blood pressure (−7 mm Hg, P=0.009 and −3 mm Hg, P=0.04, respectively), blood pressure dipping, and left ventricular diastolic function. In conclusion, PFO closure in OSA patients improves sleep-disordered breathing and nocturnal oxygenation. This translates into an improvement of endothelial function and vascular stiffening, a decrease of nighttime blood pressure, restoration of the dipping pattern, and improvement of left ventricular diastolic function.

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Key Words: arterial hypertension ■ endothelial dysfunction ■ hypoxemia ■ left ventricular diastolic function ■ obstructive sleep apnea ■ patent foramen ovale

Obstructive sleep apnea (OSA) is characterized by intermittent hypoxemia and associated with increased prevalence of vascular dysfunction and arterial hypertension, but the underlying mechanisms are incompletely understood.1 In OSA, apneas are related to excessive throat muscle relaxation with consequent inspiratory efforts against the closed glottis, finally resulting in the patient’s arousal associated with sympathetic activation and hyperventilation. The hyperventilation, in turn, contributes to the next apnea by reducing the arterial partial pressure of CO2 toward the apnea threshold. In this scenario, arterial oxygen desaturation plays a pivotal role by narrowing the gap between the eupneic and apneic CO2 pressure level, thereby rendering the CO2-controlled breathing regulation more unstable and, thus, prone to periodic breathing.2 In patients with OSA, the presence of patent foramen ovale (PFO) is associated with a marked increase in the frequency and severity of nocturnal oxygen desaturations.1 This could be related, at least in part, to right to left shunting across a PFO, as evidenced by invasive hemodynamic measurements in healthy humans, demonstrating that during the onset of simulated OSA, the right atrial pressure exceeds left atrial pressure in response to the steep decline in intrathoracic pressure.4 Improvement of arterial oxygen saturation by PFO closure may prevent this problem.

We recently reported preliminary findings showing that PFO closure in patients with newly diagnosed OSA was associated with a reduction of nocturnal apnea–hypopnea events and oxygen desaturations and decreased pulmonary artery pressure.5 Moreover, circumstantial evidence shows that intermittent hypoxia is associated with systemic endothelial dysfunction and arterial hypertension.6,7 In line with these observations, systemic endothelial function is impaired in OSA patients without any traditional cardiovascular risk factors.6 Systemic endothelial dysfunction precedes the development of arteriosclerosis and contributes to the pathogenesis of arterial hypertension.8 Accordingly, the prevalence of arterial
hypertension is increased in OSA, and resistant hypertension is often found in these patients.\textsuperscript{8,10} We hypothesized that PFO closure in newly diagnosed OSA patients improves endothelial function, blood pressure (BP), and cardiac function by reducing the number of apnea–hypopnea events and the severity of oxygen desaturations. To test this hypothesis, we searched for PFO in patients with newly diagnosed OSA and performed cardiovascular assessment, including systemic vascular function, 24-h ambulatory BP monitoring, and transthoracic echocardiography. Patients with PFO underwent initial device closure, and the others served as control group. Conventional treatment for OSA was postponed for 3 months in both groups, and polysomnographic and cardiovascular examinations were repeated at the end of the follow-up period.

Methods

Study Design and Participants

This was a prospective, open-label interventional clinical trial in 51 consecutive patients with newly diagnosed OSA in whom we searched for PFO between September 2010 and November 2013. After baseline sleep and cardiovascular evaluation, the 17 patients with PFO underwent initial device closure, and the 34 patients without PFO served as control group. Conventional treatment for OSA was postponed for 3 months in both groups, and polysomnographic and cardiovascular examinations were repeated at the end of the follow-up period. Inclusion criteria for the study were newly diagnosed mild to severe OSA, age ≥18 years, and written informed consent for study participation. Exclusion criteria were pulmonary disease other than OSA associated with oxygen desaturation, central sleep apnea syndrome, pulmonary hypertension, intracardiac shunt other than via PFO, severe valvular heart disease, body mass index ≥40 kg/m\textsuperscript{2}, and contraindication to transesophageal echocardiography (TEE).

The study protocol was approved by the ethics committee of the University of Bern, Switzerland. All included patients gave written informed consent to participate.

Study Protocol

See online-only Data Supplement.

Assessment of Obstructive Sleep Apnea by Overnight Polysomnography

Six electroencephalograms, 2 electrooculograms, electromyograms, thoraco-abdominal movements (respiratory inductive plethysmography), electrocardiography, and the patient’s posture were recorded. Nasal airflow was monitored using a nasal prong device, and arterial oxygen saturation was measured using finger pulse oximetry. Sleep state was recorded using the standard placements of electroencephalogram (C4/A1, F4/A1, and O1/A2), left and right electrooculograms, and submental electromyogram according to the classification of the American Academy of Sleep Medicine.\textsuperscript{12} All measurements were recorded with a computerized recording system (N7000, Embla, Broomfield, CO). Apnea was defined as cessation of oro-nasal airflow ≥10 s, and hypopnea as a ≥30% reduction from baseline of oro-nasal airflow for ≥10 s that was associated with ≥4% oxygen desaturation from pre-event baseline.\textsuperscript{13} Apnea–hypopnea index (AHI) was calculated as the mean number of apneas and hypopneas per hour, and apnea index was calculated as the mean number of apneas per hour between lights off and on. Severity of OSA was classified based on the AHI (number of apneas plus hypopneas per hour of sleep): mild, AHI 5 to 15; moderate, AHI 16 to 30; and severe, AHI ≥30. Analysis of polysomnography was performed automatically and corrected manually by investigators blinded to the PFO closure being present or not, allowing differentiation between obstructive and central apnea according to standard criteria. Central apnea was defined as 50% to 80% of observed apneas being of central origin (ie, cessation of airflow during sleep without respiratory effort).

Search for PFO and PFO Closure

Transesophageal Echocardiography

Before intubation of the TEE probe, the epipharynx was anesthetized using lidocaine hydrochloride 10% spray. A 3-lead ECG and BP were monitored during TEE. As sedative medication, intravenous midazolam 1 to 3 mg was used in all of the study subjects. TEE was performed in the left lateral supine position using a Philips iE33 ultrasound system with a multiplane 3.5- to 8-MHz probe. Documentation of PFO status occurred in the transversal, short axis, and longitudinal (Figure 1) image planes. The echocardiographic contrast medium for the detection of a right-to-left atrial shunt consisted of an ad hoc sonicated mixture of 0.5 mL air and 4.5 mL of gelatin containing plasma expander. Echocardiographic contrast tests were performed in the 2

Figure 1. Transesophageal echocardiography long-axis images as obtained without echo contrast bubbles (A) in a patient with patent foramen ovale (arrow). The lower panel images show the bulging of the interatrial septum toward the right atrium (RA; B) and the bulging of the interatrial septum toward the left atrium (LA; C) with spontaneous right-to-left echo contrast shunt in this patient with atrial septal aneurysm.
mentioned image planes by injection of 5 mL contrast into the right antecubital vein. Using a Valsalva maneuver (strain phase starting simultaneously with the contrast bolus injection), a leftward deviation of the interatrial septum in the fossa ovalis region was observed immediately after release of the Valsalva strain phase (lasting 5 to 10 s). The diagnosis of PFO required the crossing of bubbles from the right to the left atrium (Figure 1) within 4 heartbeats after the release of the Valsalva strain phase. The degree of PFO was qualitatively characterized by a score of 0 to 3, with a score of 1 representing the crossover of a few single bubbles and a score of 3 representing the shunt of an entire cloud of bubbles (Figure 1).

PFO Device Closure
After the application of 5000 U of intravenous heparin, a 6F catheter with a guidewire introduced from the right femoral vein was used to probe the PFO. Then, a 9F long sheath was inserted. The PFO occluder device (Amplatz PFO Occluder; St Jude Medical, Plymouth, MN; 25–35 mm in diameter depending on the size of the PFO) was delivered through the sheath and placed in the PFO under fluoroscopic guidance according to device-specific implantation recommendations. Before release of the PFO occluder, device position was checked by right atrial contrast angiography to delineate the atrial septum. All patients were treated with acetylsalicylic acid 100 mg and clopidogrel 75 mg once daily for 1 month followed by acetylsalicylic acid 100 mg/d until 6 months after PFO closure. Exactly 3 months following PFO device occlusion, TEE was repeated to search for the presence of residual right-to-left shunts.

Cardiovascular Evaluation
All cardiovascular studies were interpreted by investigators who were blinded to the PFO closure being present or not.

Assessment of Systemic Endothelial-Dependent and -Independent Function
Systemic conduit artery endothelial function was assessed using the flow-mediated diameter increase of the brachial artery in response to reactive hyperemia by high-resolution ultrasound and wall tracking as previously described. For details see online-only Data Supplement.

Assessment of Aortic and Carotid Stiffness
Aortic stiffness was assessed noninvasively by measuring carotid-femoral pulse wave velocity using the Complior device (Artech Medical, Pantin, France) as described previously. For details, see online-only Data Supplement.

Assessment of Carotid Intima-Media Thickness
Carotid intima-media thickness (IMT) was measured as previously described. For details see online-only Data Supplement.

Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>PFO Closure (n=14)</th>
<th>No PFO (n=26)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54±12</td>
<td>54±9</td>
<td>0.89</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31.1±3.8</td>
<td>30.7±4.6</td>
<td>0.77</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>12 (86)</td>
<td>22 (85)</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>2 (14)</td>
<td>3 (12)</td>
<td>1.0</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>10 (71)</td>
<td>19 (73)</td>
<td>1.0</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>6 (43)</td>
<td>10 (38)</td>
<td>1.0</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>5 (36)</td>
<td>11 (42)</td>
<td>0.75</td>
</tr>
<tr>
<td>Diuretic</td>
<td>4 (29)</td>
<td>7 (27)</td>
<td>1.00</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>1 (7)</td>
<td>3 (11)</td>
<td>1.00</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>3 (21)</td>
<td>6 (23)</td>
<td>1.00</td>
</tr>
<tr>
<td>Lipid-lowering drug</td>
<td>10 (71)</td>
<td>18 (69)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; and PFO, patent foramen ovale.
patients refused to undergo follow-up examination and were, thus, defined as dropouts. Hence, 40 patients were finally analyzed for the study, 14 in the group with PFO closure and 26 in the control group without PFO. Data on AHI, pulmonary artery pressure, and 24-h nighttime systolic BP have been previously published in form of a research letter.5

Patient Characteristics

Participants with and without PFO were comparable regarding age, height, body mass index, number of cardiovascular risk factors, and use of cardiovascular drugs (Table 1).

Cardiovascular Parameters at Baseline

With the exception of a significantly higher right ventricular–right atrial systolic pressure gradient in participants with PFO, all other variables were similar in the 2 groups (Table 2).

OSA Parameters at 3-Month Follow-Up

AHI decreased significantly during the 3-month follow-up period in patients who underwent PFO closure, whereas it remained unchanged in patients without PFO (Figure 2). Accordingly, the interindividual change in AHI differed significantly between the 2 groups (Table 3). Although AHI was not statistically different between groups at baseline or at follow-up ($P=0.59$ and 0.29, respectively), PFO closure was associated with a clinically and statistically ($P=0.007$) significant improvement of OSA severity; at baseline, 11 of 14 patients with PFO (79%) had a severe OSA (ie, AHI $>30$/h), whereas at follow-up after PFO closure, only 3 of 14 (21%) still had severe OSA. Oxygen desaturation index was not statistically different between groups at baseline or at follow-up ($P=0.59$ and 0.29, respectively), and it did not change statistically in the no PFO group ($P=0.29$). The change in oxygen desaturation index during follow-up differed significantly between the groups (Table 3).

At baseline, mean and minimal nocturnal oxygen saturation tended to be lower in the PFO closure than in the control group. These variables did not change significantly during follow-up (Table 3).
Cardiovascular Parameters at 3-Month Follow-Up

Compared with baseline, brachial artery flow-mediated vasodilation increased significantly in the PFO closure group, whereas it remained unchanged in the group without PFO (Table 2 and Figure 3A). Endothelium-independent vasodilation was comparable in the 2 groups (10.5±1.5% versus 9.9±2.8%, P=0.39, PFO closure versus no PFO). In the whole study population, there was a significant relationship between changes in AHI and increases in flow-mediated vasodilation (Figure 3B).

Carotid stiffness significantly decreased in the group with PFO closure (Table 2), whereas aortic stiffness remained unchanged and carotid IMT remained unchanged at follow-up in both groups. Central pulse pressure was comparable between the study groups at baseline and follow up (Table 2) and remained unchanged after PFO closure (47±11 vs 45±7 mm Hg, P=0.31). The distensibility coefficient, although comparable at baseline, became significantly different between the 2 groups at follow up (Table 2) because it increased significantly after PFO closure (from 29.4±16.0 to 37.0±18.0 [10−3 kPa−1], P=0.04). Nighttime systolic (−7 mm Hg, P=0.009) and diastolic BP (−3 mm Hg, P=0.04) decreased significantly in the PFO closure group, whereas it remained unchanged in the control group (Table 2 and Figure 3C). Similarly, nocturnal BP dipping increased by 5.2% in the PFO closure group (P=0.0071 for intraindividual change; Table 2) and remained unchanged (−2%-points; P=0.22) in the control group. Accordingly, at 3-month follow-up, nocturnal systolic and diastolic BP were significantly lower and nocturnal dipping greater in the PFO closure than in the control group (Table 2).

Although average 24-h HR and daytime HR remained unchanged after PFO closure, nighttime HR decreased significantly from 69±6 to 67±5 bpm (P=0.001). In line with this finding, on the HR recordings acquired during polytomography, the RR interval increased significantly after PFO closure (from 882±91 to 942±93 ms, P=0.03). Low-frequency power, high-frequency power, and low frequency/high frequency ratio remained unchanged after PFO closure (data not shown).

Early diastolic mitral annular velocity increased significantly during follow-up in the PFO closure group (P=0.0093), and it did not change in the no PFO group (P=0.59; Table 2 and Figure 3D).

Right ventricular–right atrial systolic pressure gradient decreased significantly in the PFO closure group (−4 mm Hg; P=0.009) but remained unchanged in the control group.

Discussion

OSA is a frequent problem associated with premature vascular ageing, arterial hypertension, and increased cardiovascular morbidity and mortality, but the underlying mechanism is unclear. Here, we show for the first time that in patients with newly diagnosed moderate to severe OSA and the concomitant presence of a PFO, its closure significantly improves the cardiovascular phenotype. These favorable cardiovascular effects of PFO closure were associated with improved nocturnal breathing, suggesting the existence a possible causal link.

The presence of a PFO in OSA patients has been reported to be associated with an increased number and severity of nocturnal oxygen desaturation, and the severity of OSA was found to be related with the degree of arterial hypertension. Here, we show that PFO closure in patients with OSA induced a clinically relevant decrease of the AHI (average of −7.9 events/h), which was comparable to the one usually obtained with conventional treatment (ie, continuous positive airway pressure), and was associated with a significant decrease (from 79% to 21%) of the number of patients having severe (ie, AHI >30/h) OSA. This improvement of nocturnal breathing translated into a significant reduction in nocturnal oxygen saturation drops (ie, drops in oxygen saturation >3%h) and, most importantly, was associated with a significant increase of flow-mediated dilation of the brachial artery that was related to an improvement of endothelial function because endothelium-independent vasodilation was similar in the 2 groups. This was a robust finding because in the whole study population, there was a highly significant relationship between changes in OSA severity (ie, AHI) and improvement in endothelial function.
Systemic endothelial dysfunction is the first step in the development of arteriosclerosis and contributes importantly to the pathogenesis of arterial hypertension. Desaturation/reoxygenation sequences are a typical pattern associated with OSA and have been suggested to increase sympathetic nerve activity and oxidative stress, which, in turn, contribute to systemic vascular dysfunction and cardiovascular morbidity. The present observation of a significant decrease of average nighttime HR and RR interval increase after PFO closure could suggest that the favorable cardiovascular effects of this intervention were related, at least in part, to a reduction of sympathetic activity.

In addition to endothelial dysfunction, vascular stiffening also takes place during the early development of atherosclerosis and represents an independent predictor of future cardiovascular events in populations at risk. In line with this concept, OSA patients display increased vascular stiffening. Here, we found that in OSA patients, carotid stiffness significantly decreased 3 months after PFO closure, whereas it remained unchanged at follow-up in patients without PFO. This reduction of carotid stiffness was related to improved distensibility rather than a change in distending pressure (which remained unchanged after PFO closure). This improvement of distensibility after PFO closure may be clinically important because recent data show a relationship between impaired carotid distensibility and increased cardiovascular morbidity and all-cause mortality. Finally, atherosclerosis goes along with structural changes of the vasculature. Measurement of carotid IMT by ultrasound is the most widely used noninvasive method to assess structural changes of the systemic circulation. In the present study, no relevant changes of carotid IMT were detectable at follow-up. This is not surprising because potential improvements of structural alterations of the systemic vasculature induced by PFO closure are not expected to take place over a short time period of 3 months. OSA and arterial hypertension coexist in over half of the patients with either condition, and OSA is one of the most common causes of secondary hypertension. In line with this observation, in the present study, >85% of the OSA patients had arterial hypertension.

Figure 3. Flow-mediated vasodilation (FMD) at baseline and 3-months follow-up in patients with patent foramen ovale (PFO) and without PFO (A). Correlation between changes of apnea–hypopnea index (delta AHI, follow-up minus baseline) and FMD changes (delta FMD, follow-up minus baseline) in patients with PFO (•) and without PFO (▽; B). Systolic nighttime blood pressure (BP) at baseline and 3-months follow-up in patients with PFO and without PFO (C). Early diastolic mitral annular velocity (E') at baseline and 3-months follow-up in patients with PFO and without PFO (D). Box plots and error bars indicate the median and interquartile range and 10% and 90% confidence intervals, respectively. Cross signs indicate the mean value.
the dipping pattern. This is clinically relevant because epidemiological data show that a drop of 2 mmHg of systolic and diastolic BP result in a reduction of cardiovascular mortality of ≈7% to 10% and 20%, respectively.23 Interestingly, the antihypertensive effect of continuous positive airway pressure treatment in OSA patients is ≈2 to 3 mmHg.26,27 Long-term arterial hypertension is associated with target organ damage, and left ventricular diastolic dysfunction is an early marker for target organ damage in hypertensive patients.28 In line with this concept, in our study population, left ventricular diastolic function was impaired. Most importantly, PFO closure in OSA patients improved diastolic left ventricular function, suggesting that the favorable effects of this intervention on nocturnal BP regulation and oxygenation may translate into cardioprotection.

Previous anecdotal evidence of improvement of dyspnea and desaturation in a case report29 and improvement of symptoms and nocturnal breathing in 2 of 3 patients with OSA after PFO closure30 are consistent with the present findings. The present study was the first to search for PFO in consecutive patients with OSA and to examine the effects of its closure on nocturnal breathing, vascular function, and arterial BP while following in parallel OSA patients in whom no PFO was detected as a control group to account for the natural variation of the study end points.

Sleep-disordered breathing is a frequent syndrome in patients with cardiovascular diseases in general, and particularly, in patients with congestive heart failure, obstructive and central sleep apnea are often present simultaneously.31 In our study, the presence of central sleep apnea was an exclusion criterion. It would be interesting to investigate the effects of PFO closure on central sleep apnea in the future. Moreover, we were unable to assess whether the degree of PFO was related with the change of AHI or nocturnal oxygenation after closure because all but one of the patients studied had a PFO grade III.

PFO closure is in general safe with a low complication rate. The most relevant complications are peri-procedural events, vascular access site problems, cardiac tamponade, erosion, and embolization. In a series of 825 consecutive patients undergoing PFO closure at our institution,32 complications were present in 18 (2.2%) and included device embolization (n=5), air embolism with transient symptoms (n=5), cardiac tamponade requiring pericardiocentesis (n=1), and vascular access site problems (n=7).

Perspectives

OSA is a frequent syndrome associated with increased cardiovascular morbidity and mortality. The presence of PFO is associated with more severe OSA. Here, we found that PFO closure in OSA patients improved sleep-disordered breathing and nocturnal arterial oxygenation. These improvements of nocturnal breathing were associated, 3 months after PFO closure, with a significant attenuation of endothelial dysfunction and vascular stiffening, a decrease of nighttime BP and restoration of its dipping pattern, and an improvement of left ventricular diastolic function. We speculate that PFO closure in OSA patients is a valid alternative to conventional therapy, particularly in those who are intolerant to continuous positive airway pressure therapy and dental device treatment. Larger randomized studies should confirm our results and assess the impact of PFO closure on cardiovascular morbidity and mortality in this growing population at high cardiovascular risk.

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Disclosures

None.

References


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PATENT FORAMEN OVALE CLOSURE IN OBSTRUCTIVE SLEEP APNEA IMPROVES BLOOD PRESSURE AND CARDIOVASCULAR FUNCTION

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1) Expanded materials and methods

1.1. Study protocol

Once the diagnosis of OSA was established by polysomnography, patients willing to participate in the study underwent transthoracic echocardiography before performing TEE. During the first visit after study inclusion, assessment of systemic vascular function was carried out. At the end of this visit, 24h ABPM was performed. Three to 10 days after this visit, patients with diagnosed PFO underwent percutaneous PFO closure. After PFO closure, a control TTE to confirm the correct position of the device was done during the same day in all patients. After 3 months, in all patients the following procedures were repeated: polysomnography, 24-hour ABPM, systemic vascular function and TTE. In patients with PFO closure, TTE was performed followed by TEE. During the entire follow-up period, there was no change in cardiovascular drug therapy and non-invasive ventilatory therapy was deferred.

1.2. Methods for assessment of vascular function

Assessment of systemic endothelial-dependent and -independent function

The brachial artery was identified approximately 5cm above the antecubital fossa with a high-resolution ultrasound device (Esaote MyLab30 Gold, Esaote SpA, Italy). Images of the artery were analyzed using an edge detection software with a system for real-time measurement of the brachial artery diameter in B-mode ultrasound images (Cardiovascular Suite, Quipu, Pisa, Italy) for determination of the baseline diameter of the vessel. Then, a forearm pressure cuff was inflated to 250mmHg for 5 minutes. After deflation of the cuff, the hyperemia-induced change of the brachial artery diameter was recorded continuously during the entire examination of 9 minutes. Flow-mediated dilatation was expressed as the maximal percent change in vessel diameter from baseline.

Endothelium-independent dilation change of the brachial artery was assessed at follow-up by measuring the increase of the brachial artery diameter evoked by oral glyceryl-trinitrate (GTN 50 μg, UCB-Pharma, Bulle, Switzerland).

Assessment of aortic and carotid stiffness

Carotid and femoral artery waveforms were simultaneously recorded with mechano-transducers directly applied to the skin over the arteries and the mean wave transit time for 10 heart beats was calculated by the system software using the foot-to-foot method. To determine the pulse wave velocity, the surface distance between the recording sites was measured. Carotid stiffness was assessed non-invasively immediately after carotid tonometry with the SphygmoCor system (AtCor Medical, Sydney, Australia) by measuring parameters of local elasticity with a validated edge detection system (Carotid Studio®, Cardiovascular Suite; Quipu srl, Pisa, Italy) applied to B-mode ultrasound sequences of longitudinal section of the carotid artery obtained using an Esaote 30 MyLab Gold (Esaote SpA, Genova, Italy). To determine carotid pulse pressure (PP), carotid distension waveforms were obtained and rescaled using brachial distension waveforms. The distensibility coefficient (DC) was calculated using the following equation: DC=(ΔA/A)/cPP, where ΔA=stroke change (i.e. distension) of the carotid artery cross sectional area, A=total diastolic carotid artery cross sectional area, cPP=carotid PP. Carotid PWV was calculated using the Bramwell-Hill equation (carotid PWV=√(1/(ρ*DC)), where ρ=density of blood, assumed to be 1050 kg/m³).
Assessment of carotid intima-media thickness.
Briefly, after identification of the carotid bulb, the segments of the right and left common carotid artery 1 to 2 cm proximal to the bulb were scanned to identify the optimal angle of incidence in accordance with current guidelines. Carotid intima-media thickness (IMT) was measured using radiofrequency signals with a 21 µm resolution (RF QIMT, Esaote, Genova, Italy).