Upper extremity blood pressure difference in patients undergoing carotid revascularization

Short title: Blood pressure difference in patients undergoing carotid revascularization

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What this paper adds

This study reports that one out of every five patients with carotid stenosis amenable to surgery exhibit inter-arm SBP difference >15 mmHg and approximately one fifth of those with inter-arm SBP difference suffer from subclavian or innominate artery stenosis. Our results therefore affirm the clinical need for inter-arm BP differences in patients undergoing carotid revascularization, especially in the postoperative phase in the prevention of cerebral hyperperfusion.

Abstract:

Introduction

Blood pressure (BP) regulation is important in patients with carotid artery atherosclerotic disease. Concomitant subclavian artery stenosis (SAS) might underestimate the true systemic BP monitoring in these patients. We aimed to assess the prevalence of inter-arm BP difference in patients undergoing carotid intervention and it's association with ipsilateral significant subclavian stenosis and clinical outcome.

Methods

Bilateral BP measurements and vascular imaging (CTA and MRA) of both subclavian arteries and the innominate artery were assessed in 182 symptomatic patients with carotid artery stenosis undergoing revascularization in the International Carotid Stenting Study (ICSS). Data were separately analysed according to previously described cut off values for systolic BP (SBP) differences of ≥ 10 and < 15 mmHg, ≥ 15 and < 20 mmHg or ≥ 20 mmHg. We defined significant SAS as a >50% diameter reduction.

Results

39/182 (21%) of patients showed an inter-arm difference in SBP exceeding 15 mmHg. The mean inter-arm SBP difference associated with ipsilateral SAS was 14 mmHg. SAS was present in 21/182 (12%) patients. Only two patients (1%) had bilateral stenotic disease. An inter-arm SBP difference of ≥ 20 mmHg was associated with unilateral SAS (RR 11.8; 95% CI 3.2 – 43.1) with a sensitivity of 23% and a specificity of 98%. Patients were followed up for a median of 4.0 years (IQR 3.0 – 6.0; maximum 7.5). Risk of stroke or death during follow-up was 20.0% (95% CI 11.1-28.9) in patients with and 15.1% (95% CI 12.3-17.9) in patients without SAS (p=0.561). The length of stay in hospital was longer in patients with significant SAS (5.0 days; SD 4.9 vs. 2.7 days; SD 4.3 [p=0.035])

Conclusion

Our study is the first to affirm the clinical need for inter-arm BP differences in patients undergoing carotid revascularization, especially in the postoperative phase in the prevention of cerebral hyperperfusion.

Introduction

Blood pressure (BP) regulation plays an important role in the management of patients with cerebrovascular disease. A recent analysis showed that adequate implementation of 2014 hypertension guidelines could potentially prevent 37,400 strokes annually in the U.S.[1]

Haemodynamic instability is observed in 13% - 23% of patients undergoing carotid endarterectomy (CEA) [2,3,4,] and is associated with poor perioperative outcomes as well as an increased 1-year stroke or death rate. [3,4] Peri-procedural haemodynamic depression in patients treated by carotid artery stenting (CAS), is associated with an excess of new ischaemic brain lesions. In general, patients undergoing carotid intervention under general anaesthesia are more likely to be exposed to intra-procedural hypotension and post-procedural hypertension.[5] Intra- and post-procedural management should therefore include careful control of BP to protect patients from severe periprocedural hypotension and postoperative cerebral hyperperfusion. [6]

Current guidelines suggest non-invasive bilateral BP measurement at the level of the arteria brachialis.[7,8] However, in daily practice these guidelines may be neglected with BP often being measured only in the arm that is most accessible at the time of examination. Systolic BP difference is often related to anatomic correlation between atheromatous disease in the carotid, subclavian or the innominate artery. Patients with carotid artery disease often have multilevel atherosclerotic pathology including the origin of the subclavian arteries. In bilateral compromised outflow in the subclavian arteries, even in the presence of a left right BP difference, this may still underestimate the central aortic pressure. Given that guidelines recommend treatment of hypertension to specific targets on the basis of BP readings, underestimation of BP might lead to inadequate treatment of hypertension. To the best of our best knowledge, no previous study has ever focused before on the existence of BP differences in patients undergoing carotid revascularization.

We aimed to assess the prevalence of baseline upper extremity BP difference in relation to the presence of subclavian artery or innominate artery stenosis in patients undergoing carotid revascularization.

Methods

Patients

All patients participating in the International Carotid Stenting Study (ICSS), who were treated in the University Medical Center Utrecht (UMCU) between 2003 and 2009, were included in this study. The methods of this multicentre RCT (ISRCTN 25337470) have been described previously. In summary, patients with recently symptomatic moderate or severe carotid stenosis (≥50% reduction of the lumen diameter according to the NASCET method) were randomly assigned to receive either carotid artery stenting or endarterectomy in a 1:1 ratio. In ICSS vascular imaging of the cerebral and supra-aortic vessels was required prior to randomization. For the purpose of this study, patients were only included if bilateral BP measurements were available and if the quality of vascular imaging allowed us to reliably detect and quantify the degree of potential subclavian stenosis. A total of 1713 patients were enrolled in ICSS, of which 270 patients were randomized in the UMCU.

Blood pressure measurements

Systolic blood pressure (SBP) and Diastolic blood pressure (DBP) were measured non-invasively at the time of randomization or during the patient's first visit to the outpatient clinic. Measurements were done according to physician preference using either manual or automated devices. Although this was not systematically recorded, the automatic device was usually the preferred method with the patient in supine position. The inter-arm BP difference was calculated using the following formula: $[SBP_{highest}] – [SBP_{lowest}]$. Data were separately analysed according to previously described cut off values for SBP differences of ≥ 10 and < 15 mmHg, ≥ 15 and < 20 mmHg or $\geq$ 20 mmHg.[9,10,11] An difference in SBP of <10 mmHg was considered an equal BP in both arms.

Assessment of baseline imaging

Among 270 patients, 46 did not have documented bilateral BP assessment. Available vascular imaging at randomisation did not allow assessment of the subclavian arteries, in 42 patients. Of the remaining 182 patients, vascular imaging was performed with Computed Tomography Angiography (CTA) in 104 patients (57%), Magnetic Resonance Angiography (MRA) in 77 patients (42%) and conventional angiography in one patient (0.5%). The assessment of baseline imaging was performed by one radiologist (SP), who was blinded to treatment allocation and the presence of BP difference. The extent of stenosis for both subclavian arteries and the innominate artery (i.e. the brachiocephalic trunk) was assessed, using criteria based on the North American Symptomatic Carotid Surgery Trial (NASCET). We classified patients in the following 5 categories: (1) no atherosclerotic lesion; or stenosis measuring: 2) 1-24%; 3) 25-49%; 4) 50%-74%; and 5) 75-100%. We defined significant stenosis as a reduction in vessel diameter of > 50%.

Procedural (<30 days) and long term outcome

In ICSS major outcome events were adjudicated by an independent endpoint committee that was unaware of treatment allocations. Stroke was defined as a rapidly developing clinical syndrome of focal disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin. For the present analysis, medical records were reviewed to assess the number of patients in whom treatment of BP was necessary after the procedure. We further classified patients according to the location at which BP treatment was given: vascular ward or medical care unit.

Statistical Analysis

We compared SAS as a dichotomous outcome, between groups defined by inter-arm SBP difference with a threshold of either ≥ 10 mmHg, ≥ 15 mmHg and ≥ 20 mmHg.[9,10,11] A Chi-square test was used to compare the presence of ipsilateral SAS between patients with and without inter-arm SBP difference. Continuous variables were compared with the Mann-Whitney U test. Relative risks for the presence of ipsilateral SAS in relation to inter-arm SBP difference were calculated. *P*- values of <0.05 were considered statistically significant.

Results

Inter-arm blood pressure differences

The mean SBP in 182 patients was 165 mmHg (range 100 - 230). For 116 patients (64%), SBP was equal (<10 mmHg) in both arms (mean SBP 164, range 107 - 220). In the remaining 96 patients, inter-arm blood pressure difference in SBP ranged from 1 mmHg to 35 mmHg with a mean inter-arm SBP difference of 6.94 mmHg. In 39/182 (21%) the inter-arm SBP difference exceeded the 15 mmHg (range 15 – 35) (table 1).

Subclavian artery and innominate artery stenosis

Overall, a >50% subclavian or innominate stenosis was present in 21/182 patients (12%). In 8 patients unilateral disease consisted of a right subclavian or innominate artery stenosis. In 11 patients unilateral disease consisted of a left subclavian stenosis. Two patients (1%) had bilateral stenotic disease. In 1 patient bilateral disease consisted of a left subclavian stenosis and innominate artery stenosis. The remaining patient presented with a bilateral SAS. (table 2) No reversed flow in the vertebral arteries was detected among the 21 patients with >50% subclavian or innominate stenosis.

Inter-arm blood pressure differences in relation to subclavian stenosis

In 10/21 patients with SAS, a lower SBP was measured ipsilateral to the stenosis in cases of unilateral disease and ipsilateral to the most severe stenosis in cases of bilateral disease. In the remaining 11 patients, no BP difference (n=8) or a higher BP was measured ipsilateral to the stenosis (n=3). The sensitivity of the finding of a lower

SBP to detect ipsilateral SAS with a threshold of ≥10 mmHg was 14%, for a threshold of ≥15 mmHg 18% and for a threshold of ≥ 20 mmHg 23%. Specificity was respectively 99%, 98% and 98% (table 3). The mean inter-arm SBP difference in patients with SAS was 14.21 mmHg. On average, the mean inter-arm SBP difference was higher in those patients with more severe stenosis (table 4). We found a RR of 11.8 (95% CI 3.2 – 43.1) for SAS of more than 50% and a SBP difference of ≥ 20 mmHg. RR measurements for other SBP thresholds are presented in table 5.

Procedural (<30 days) and long-term outcome

In our cohort, a total of 9 (4.9%) procedural strokes occurred. The most likely mechanism of stroke in these patients were as follows: hyperperfusion (n=3), hypoperfusion (n=2), thrombo-embolic (n=2), ipsilateral carotid occlusion (n=1), cardio-embolic (n=1). The rate of procedural stroke was non-significantly higher in patients with SAS compared to patients without SAS, respectively 2/21 (9.5%) and 7/161 (4.3%) (*p=0.62*). Among 3/9 (33%) patients with procedural stroke a SBP difference was present. All strokes in patients with a SBP difference were caused by hyperperfusion. Patients were followed up for a median of 4.0 years (IQR 3.0 – 6.0; maximum 7.52). Kaplan Meier life table analysis showed a similar cumulative risk of stroke or death during follow-up in patients with (20.0%; 95% CI 11.1-28.9) and without SAS (15.1%; 95% CI 12.3-17.9) (*p=0.56*). In patients with a SBP difference of ≥ 15 mmHg the cumulative risk of stroke or death during follow-up was 13.2% (95% CI 7.7-18.7) as compared to 16.3% (95% CI 13.2-19.4) in patients with equal SBP or a SBP difference of ≤ 15 mmHg *(p=0.64).*

Blood pressure management in the procedural (<30 days) period

In 168 of 182 patients (20 with and 148 without significant SAS), data was available on peri-procedural BP management. The amount of patients in which a BP intervention was encountered requiring medical treatment was similar in patients with (5/20; 25%) and without (24/148; 16%) SAS (*p=0.51*). Ten percent (2/20) of patients with SAS were admitted to the medium care unit for intravenous BP regulation compare to 4% (6/148) of patients without SAS (*p=0.50*). Patients with SAS admitted to the medium care had a longer hospital stay (5.0 days; SD 4.9 vs. 2.7 days; SD 4.3 [*p=0.04*])

Discussion

As far as we are aware, the present study was the first to assess the prevalence of upper extremity BP differences in relation to SAS in patients undergoing carotid revascularization. One out of five patients showed an interarm SBP difference exceeding 15 mmHg. An inter-arm SBP difference of 15 mmHg or higher was associated with ipsilateral SAS > 50%, but showed a low sensitivity and high specificity. In this cohort, the prevalence of patients with a bilateral compromised outflow in the subclavian artery was very low (1%). No association was found between SAS and 30-day stroke rate or stroke or death rate during follow-up, but the mean length of stay in hospital was longer in these patients. The prevalence rates presented in our study are in agreement with the findings in previous secondary care populations. [12,13]

A recent meta-analysis investigated whether an association between SBP differences and central or peripheral vascular disease existed. [9] The pooled findings of five studies, including individuals with raised cardiovascular risk, showed a strong association between angiographically proven SAS and an inter-arm SBP difference of 10 mmHg or more (RR 8.8, 95% CI 3.6 – 21.2).[9] The RR for a threshold of 10 mmHg in our study was twice as high, but should be interpreted cautiously, because of the width of confidence intervals.

In nine out of ten patients with equal SBP, no significant SAS was present. However, even in patients with equal BP, although very scarce, bilateral subclavian stenosis can still be present. In this subgroup of patients, BP measurements represent a lower value than the true systemic BP. Furthermore, potentially co-existing aortic or ilio-femoral stenosis may influence the reliability of BP measurements at the lower extremity. In such cases, intravascular BP readings should be performed to reliably detect haemodynamic disturbances during the procedure.

In the International Carotid Stenting Study (ICSS) haemodynamic depression occurred in 13.8% of cases after carotid artery stenting (CAS), and in 7.2% of cases after carotid endarterectomy (CEA). In patients treated by CAS, peri-procedural haemodynamic depression was associated with an excess of new ischaemic brain lesions.[2,15] A further detailed analysis of procedural strokes in this randomized trial showed that one third of procedural strokes were caused by peri-procedural haemodynamic disturbances, suggesting that careful attention to blood pressure control could further lower the risk of this procedural complication.[14] In this context it is interest to note that in our study, all patients with procedural strokes caused by hyperperfusion, were known to have a SBP difference. While all patients with procedural strokes not related to hyperperfusion had equal SBP.

Our study has several limitations. First of all, due to its retrospective character bilateral BP measurements were not performed in 46 patients. This finding emphasizes the need for firm recommendations to measure blood pressure on both arms in all CEA patients. Secondly, the method of measurement used was sequential rather than simultaneous. In sequential blood pressure measurement the so called ‘white coat-effect’ could contribute to the amount of blood pressure difference recorded, in which the first measurement is higher than the second.[16] However, our results showed an association between inter-arm blood pressure difference in SBP and subclavian stenosis, making it less likely that recorded differences were attributable to a ‘white coat-effect’. Thirdly, the mean SBP in our subgroup of patients was much higher than the mean SBP in ICSS (165 mmHg vs 147 mmHg), indicating poor control of hypertension in our patients.

In conclusion, within this single centre study about one out of every five patients with carotid artery stenosis undergoing revascularization within an international RCT, did not have a documented bilateral assessment of the blood pressure. Of those patients with bilateral measurements we found a high prevalence of inter-arm blood pressure difference sin SBP and this was strongly associated with the presence of ipsilateral significant subclavian stenosis. In line with guidelines on the treatment of patients undergoing carotid revascularization this study reaffirms the need for non-invasive bilateral blood pressure measurements in all patients undergoing carotid intervention. The prevalence of patients with a bilateral compromised outflow in the subclavian stenosis was very low in our cohort. This suggests that it is safe to consider the highest measurement as the true blood pressure.

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Disclosures

The authors have no conflicts of interest.

Legends of Figures

Figure 1 Flow chart of patients included in the present analysis

Table 1 Number of patients with inter-arm blood pressure differences (SBP, systolic blood pressure difference)

	Number of patients (%) (n=182)
SBP inter-arm difference	
- <10 mmHg	116 (64)
- 10 - 14 mmHg	27 (15)
- 15 - 19 mmHg	9 (5)
- ≥ 20 mmHg	30 (16)

Table 2. Sites and number of patients (%) with significant (>50%) stenosis (n=182)

Site of stenosis	**right sided stenosis**	**left sided stenosis**	**bilateral stenosis**
- Subclavian stenosis	6 (3.0%)	11 (6.0%)	1 (0.5%)
- Innominate stenosis	2 (1.0%)	n/a	n/a
- Left subclavian and innominate stenosis	n/a	n/a	1 (0.5%)
- Bilateral subclavian and innominate stenosis	n/a	n/a	0 (0.6%)

Table 3 Systolic blood pressure interarm differences in relation to ipsilateral haemodynamic significant (>50%) subclavian or innominate stenosis.

	≥ 10 mmHg n=66 (%)	≥ 15 mmHg n=39 (%)	≥ 20 mmHg n=30 (%)
- Ipsilateral stenosis	9 (14)	7 (18)	7 (23)
- No ipsilateral stenosis	57 (86)	32 (82)	23 (77)

Table 4. Comparison of mean systolic blood pressure (SBP) difference in patients with and without stenosis.

	Mean SBP difference (mmHg)		
	With stenosis	without stenosis	p-value*
- Stenosis 0-25%	6.09	7.80	0.224
- Stenosis 25-50%	4.78	7.94	0.045
- Stenosis 50-75%	12.22	6.59	0.014
- Stenosis 75-100%	23.33	6.87	0.002

* p-value derived by use of the t-test comparing mean SPB difference between patients with and without stenosis.

Table 5. Systolic blood pressure inter-arm difference in relation to ipsilateral subclavian stenosis

	Stenosis / total		*Relative Risk (95% CI)
	Difference ≥ mmHg	Difference < mmHg	
- ≥ 10 mmHg	9 / 66	1/116	15.8 (2.0 – 122.1)
- ≥ 15 mmHg			

	7/39	3/143	8.6 (2.3 – 31.6)
- ≥ 20 mmHg			
	7/30	3/152	11.8 (3.2 – 43.1)

* Relative risk ratios for ipsilateral subclavian or innominate stenosis in patients with and without differences in systolic blood pressure of respectively ≥10 mmHg, ≥15 mmHg and ≥20 mmHg between arms.

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