

# Recurrent Blood Pressure Rise after Treatment with Anti-vascular Endothelial Growth Factor Agents

## Wiederholter Blutdruckanstieg nach Injektionen mit Anti-vascular endothelial Growth Factor

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### Schlüsselwörter

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### ABSTRACT

**Background** It has previously been shown that the process of anti-vascular endothelial growth factor (VEGF) injections can lead to a significant increase of blood pressure. The aim of this study was to investigate whether this blood pressure increase was reproducible with repeated anti-VEGF injections.

**Patients and Methods** Patients with a systolic blood pressure of  $\geq 180$  mmHg during previous injections who were scheduled for further injections were asked to participate in this study. Systolic as well as diastolic blood pressure was measured before, during, and after the intravitreal injection process.

**Results** Thirty-nine patients (21 females, 18 males) with a mean age of 75 years (range 34–94 years) were included in

this extension of the FEAR study. At first, clinical systolic blood pressure rose from an average of  $157.3 \pm 5.9$  mmHg to  $175 \pm 6.7$  mmHg at the time of the injection process ( $p < 0.01$ ). Diastolic blood pressure rose from an average of  $75.72 \pm 4.2$  mmHg to  $84.44 \pm 7.3$  mmHg ( $p < 0.13$ ) at the time of the injection process. Overall, the majority of the participants (56%,  $N = 22$ ) had a systolic blood pressure of  $\geq 180$  mmHg.

**Conclusions** Our results show that the blood pressure increase occurs persistently during the injection process in some patients. Repeated episodes of severe hypertension may predispose patients to cardiovascular events, especially those with concomitant cardiovascular risk factors.

### ZUSAMMENFASSUNG

**Hintergrund** Bereits vorgängig wurde gezeigt, dass der Verabreichungsprozess von Injektionen mit Anti-vascular endothelial Growth Factor (Anti-VEGF) zu einem signifikanten Blutdruckanstieg führen kann. Das Ziel dieser Studie war die Untersuchung der Reproduzierbarkeit dieses Blutdruckanstiegs mit wiederholten Anti-VEGF-Injektionen.

**Patienten und Methoden** Patienten mit einem systolischen Blutdruckwert  $\geq 180$  mmHg während vorhergehender Injektionen in der FEAR-Studie, für welche weitere Injektionen geplant waren, wurden gefragt, ob sie an der Studie teilnehmen wollen. Der systolische wie auch der diastolische Blutdruck wurden vor, während und nach dem intravitrealen Injektionsprozess gemessen.

**Ergebnisse** 39 Patienten (21 Frauen, 18 Männer) mit einem Durchschnittsalter von 75 Jahren (im Alter von 34 bis 94 Jahren) wurden in dieser Erweiterung der FEAR-Studie eingeschlossen. Der systolische Blutdruck stieg ausgehend von einem Mittelwert von  $157 \pm 5,9$  mmHg bei Ankunft der Patienten auf  $175 \pm 6,7$  mmHg zum Zeitpunkt des Injektionsprozesses an ( $p > 0,01$ ). Der diastolische Blutdruck stieg ausgehend von einem Mittelwert von  $75,72 \pm 4,2$  mmHg bei Ankunft der Patienten auf  $84,44 \pm 7,3$  mmHg zum Zeitpunkt des Injektionsprozesses an ( $p < 0,13$ ). Insgesamt zeigte die Mehrheit der Teilnehmer (56%,  $n = 22$ ) einen systolischen Blutdruck von  $\geq 180$  mmHg.

**Schlussfolgerungen** Unsere Resultate zeigen, dass der Blutdruckanstieg während des Injektionsprozesses bei einigen Patienten konstant auftritt. Wiederholte Episoden von schwerer

Hypertonie können zu kardiovaskulären Ereignissen prädisponieren, besonders bei Patienten mit zusätzlich begleitenden kardiovaskulären Risikofaktoren.

## Background

Age-related macular degeneration (AMD), diabetic macular edema (DME) as well as macular edema due to retinal vein occlusions (RVO) [1, 2] are three of the most common macular diseases in the Western world. All, if left untreated, may lead to severe vision loss. With the introduction of anti-vascular endothelial growth factor (Anti-VEGF) agents about two decades ago, a highly effective drug for the treatment of neovascular AMD as well as macular edema secondary to diabetes and vein occlusion has become available. Since then, many trials have shown that injections with Anti-VEGF agents may prevent further loss of visual acuity (VA) or may even lead to an increase of VA [3–6]. Anti-VEGF treatment has emerged as one of the most favorable therapies for macular diseases and many people today receive intravitreal injections with Anti-VEGF agents.

Due to this success, the number of injections has increased considerably. There has been an increasing debate about potential systemic side effects, such as an increased risk of systemic vascular events [7]. In addition to systemic exposure to anti-VEGF [8], other factors such as cardiovascular risk factors or, possibly, repeated blood pressure decompensation may be responsible for the observed increase in cardiovascular events in patients receiving anti-VEGF injections [9].

In a previous study, we were able to show an association of intravitreal injections with a transient, significant increase in blood pressure. In this recent study, 11% of the participants had a systolic blood pressure of  $\geq 200$  mmHg during the injection process [10].

The aim of the present study was to investigate whether patients experience a repeated blood pressure rise with repeated intravitreal injections.

## Participants and Methods

The study was performed according to the International Ethical Guidelines for Biomedical Research Involving Human Subjects and approved by the ethics review board of Bern, Switzerland.

The study was designed as a prospective, descriptive observational study in a tertiary referral center. All patients were previously informed about the procedures and goals of the study. Informed consent for blood pressure measurements during injections was obtained for all participants before entering the study.

Participants previously included in the “Following Excitement and Anxiety Response under intravitreal Injection – the FEAR study” who had a blood pressure of  $\geq 180$  mmHg during the first set of measurements were scheduled for further injections and included into the study. This cohort of FEAR study patients was advised to have their blood pressure checked at their general practitioner. Each participant was evaluated routinely for visual acuity and received biomicroscopic fundus examination before injection.

The protocol for blood pressure measurement was as follows: The first blood pressure measurement was taken on the right arm 30 min before injection in the waiting area (SYS & DIA 1), the second measurement 5 min before injection in the preparing room (SYS & DIA 2), the third measurement during the injection (SYS & DIA 3), and the last measurement 15 min after the injection (SYS & DIA 4). Systolic as well as diastolic blood pressure was measured with a portable noninvasive recording device.

Data analysis was performed using GraphPad Prism version 5.02 for Windows (GraphPad Software, La Jolla, CA, USA, www.graphpad.com and SigmaPlot version 11.0). Repeated measures ANOVA was used to compare data at different time points. A *p* value of  $\leq 0.05$  was considered to be statistically significant.

## Results

Thirty-nine patients, of which 54% (*N* = 21) were women and 46% (*N* = 18) were men, were included in this study. The average age was 75 years (median = 78 years, min = 34 years, max = 94 years). About one-third of these patients had neovascular age-related macular degeneration (nAMD) (36%, *N* = 14). Another third had macular edema due to retinal vein occlusions (RVO) (31%, *N* = 12), and 23% (*n* = 9) had diabetic macular edema. The majority of these patients were already familiar with the injection procedure, with an average number of 30 injections (median = 23 injections, min = 4, max = 95). The mean increase of systolic blood pressure from the first measurement to the measurement at the time of injection was significant (► **Table 1** and **2**).

Overall, the majority of all the participants (56%, *N* = 22) had a systolic blood pressure of  $\geq 180$  mmHg in one of the four measurements. However, there was no significant change in diastolic blood pressure at the four predefined time points in the study protocol (► **Table 3** and **4**).

## Conclusions

The results show that there is a significant rise in blood pressure during the intravitreal injection process. These results support the findings of the study of Berger et al. [10] and show that the blood pressure increase is reproducible and fairly consistent during the intravitreal injection process.

The question arises, whether a repeated blood pressure rise may be responsible for the higher incidence of cardiovascular incidents in a subpopulation of patients receiving anti-VEGF injections. According to the European Society of Cardiology and the European Society of Hypertension, a systolic blood pressure of  $\geq 180$  mmHg and/or diastolic blood pressure of  $\geq 110$  mmHg is called severe hypertension (Grade 3). If the increase in blood pressure is related with organ damage, the term hypertensive emergency is used [11].

► **Table 1** Systolic blood pressure values at four different time points (SYS1 – SYS4).

	SYS1 (30 min prior to injection)	SYS2 (5 min prior to injection)	SYS3 (during the injection)	SYS4 (15 min after injection)
Minimum	123	110	116	114
Median	161	166	180	165
Maximum	202	216	221	208
Mean (95% CI)	157.3 (151.5–163.2)	167 (160–173.9)	175 (168.4–181.7)	161.4 (154.6–168.3)
Std. deviation	18.1	21.45	20.59	21.11
Std. error of mean	2.899	3.434	3.297	3.38

► **Table 2** Mean differences and p values of the systolic blood pressure values at four different time points (SYS1 – SYS4).

Tukey's multiple comparisons test	Mean difference	95% CI of mean difference	Adjusted p value	Significant
SYS1 vs. SYS2	-9.641	-21.61–2.332	0.1605	No
SYS1 vs. SYS3	-17.69	-29.67–5.719	0.001	Yes
SYS1 vs. SYS4	-4.077	-16.05–7.896	0.8129	No
SYS2 vs. SYS3	-8.051	-20.02–3.922	0.3033	No
SYS2 vs. SYS4	5.564	-6.409–17.54	0.6233	No
SYS3 vs. SYS4	13.62	1.642–25.59	0.0189	Yes

► **Table 3** Diastolic blood pressure values at four different time points (DIA 1 – DIA 4).

	DIA 1 (30 min prior to injection)	DIA 2 (5 min prior to injection)	DIA 3 (during the injection)	DIA 4 (15 min after injection)
Minimum	52	51	51	56
Median	73	73	83	76
Maximum	107	158	182	128
Mean (95% CI)	75.72 (71.52–79.91)	79.08 (73.36–84.79)	84.44 (77.1–91.77)	77.54 (72.63–82.45)
Std. Deviation	12.95	17.65	22.63	15.14
Std. Error of Mean	2.073	2.822	3.624	2.425

► **Table 4** Mean differences and p values of the systolic blood pressure values at four different time points (DIA 1 – DIA 4).

Tukey's multiple comparisons test	Mean difference	95% CI of mean difference	Adjusted p value	Significant
DIA 1 vs. DIA 2	-3.359	-13.63–6.913	0.8306	No
DIA 1 vs. DIA 3	-8.718	-18.99–1.554	0.1266	No
DIA 1 vs. DIA 4	-1.821	-12.09–8.452	0.9675	No
DIA 2 vs. DIA 3	-5.359	-15.63–4.913	0.5294	No
DIA 2 vs. DIA 4	1.538	-8.734–11.81	0.9799	No
DIA 3 vs. DIA 4	6.897	-3.375–17.17	0.3046	No

It is known that repetitive hypertensive urgencies are associated with an increased risk for subsequent cardiovascular events [12]. This may be especially important for patients having repeated episodes of severe hypertension (hypertensive urgencies) and a concomitant microangiopathy, which is known to be associated with small artery fibrinoid necrosis in the kidney, retina, and brain [11].

In our study, 59% of the participants (N = 23) had an overall increase of systolic blood pressure  $\geq 20$  mmHg during the injection process. According to the ESC/ESH Guidelines, such fluctuations constitute an additional risk factor for organ dysfunction [13].

Limitations of the study are the lack of long-time monitoring, a lack of continuous blood pressure measurement 24 h before and

24 h after the injection process, and the relatively small study population as well as the absence of a sham group.

In conclusion, we were able to demonstrate that the intravitreal injection process can lead to a consistent and repeated blood pressure rise. In patients experiencing severe hypertension during the injection process and who receive anti-VEGF treatment on a regular basis, this may occur on a monthly basis. Furthermore, patients with a recent history of cardiovascular events or other concomitant risk factors, such as diabetes, may be especially at risk for developing new cardiovascular events due to a severe blood pressure rise occurring during the intravitreal injection process.

### Conflict of Interest

The authors declare that they have no conflict of interest.

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