

# Funduscopy: Yes or no? Hypertensive emergencies and retinopathy in the emergency care setting; a retrospective cohort study

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## Abstract

According to international guidelines, patients with a suspected hypertensive emergency (HE) admitted to the emergency department (ED) should undergo comprehensive evaluation including funduscopic examination. However, funduscopy is not always readily available and little is known about the prevalence of retinopathy among these patients in the ED setting. In order to characterize patients who should undergo funduscopy, we studied the prevalence, characteristics and clinical outcome in patients with a suspected HE and retinopathy grade III/IV. We conducted a retrospective cohort study of consecutive patients with severe elevation of blood pressure (BP) admitted to the ED between 2012 and 2015. Patients with a systolic blood pressure (SBP)  $\geq 180$  mm Hg or diastolic blood pressure (DBP)  $\geq 120$  mm Hg at time of presentation were included. A total of 271 patients were included, of whom 18 (6.6%; 95%CI 3.9-10.5) had a HE. In 121 patients (44.6%; 95%CI 37.1-53.3), funduscopy was performed, of whom 17 (14.0%; 95%CI 8.2-22.5) had retinopathy grade III/IV. Mean SBP and DBP were significantly higher in patients with retinopathy ( $P < .001$ ). However, retinopathy was also seen in patients with lower BP (SBP  $< 200$  mm Hg and DBP  $< 120$  mm Hg). No differences in other clinical characteristics, including visual disturbances, were found. One patient with retinopathy suffered an ischemic stroke after taking oral medication. The prevalence of retinopathy is high among examined patients. Except for higher BP, no clinical signs or symptoms are associated with the presence of retinopathy grade III/IV. We therefore conclude that funduscopic examination should be performed in every patient with a suspected HE.

## 1 | INTRODUCTION

Patients referred to the emergency department (ED) with severe elevation of blood pressure (BP) account for a large number of the

total admissions.<sup>1</sup> Severe BP elevation can lead to a hypertensive emergency (HE), which is defined as a severe rise in BP associated with acute end-organ damage.<sup>2,3</sup> In HE cerebral autoregulation, which maintains a constant cerebral blood flow, is compromised leading to cerebral hyperperfusion and edema.<sup>4</sup> In this condition, BP

[Correction added on February 8, 2021, after first online publication: The copyright line was changed.]

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control should be prompt and monitored in an ICU to avoid ongoing organ damage and mortality.<sup>5-7</sup>

According to current guidelines, patients with a suspected HE should undergo comprehensive examination.<sup>3</sup> This examination includes a funduscopy, since the presence of grade III or IV hypertensive retinopathy is a sign of microvascular dysfunction and impaired cerebral autoregulation, and can be the only sign of an ongoing HE.<sup>4,8,9</sup> Retinopathy grade III/IV is associated with both short- and long-term cerebral, renal and cardiovascular complications. Although 5-year survival of patients with retinopathy grade III/IV is improving over years, all-cause mortality in these patients is still significantly higher in comparison to hypertensive patients without retinopathy.<sup>10-13</sup>

However, immediate examination by an ophthalmologist is not always possible, especially outside office hours. In clinical practice, this often leads to the discussion whether or not to perform funduscopy, especially in patients without findings of acute damage in other end-organs. Little is known about the prevalence of retinopathy grade III/IV among patients presenting at the ED with highly elevated BP, the clinical characteristics of these patients and how retinopathy is related to other acute end-organ damage. Thus far, studies focusing on the prevalence of hypertension with retinopathy grade III/IV only comprise patients in the outpatient clinic or were based on the diagnosis malignant hypertension in which retinopathy grade III/IV is part of the definition.<sup>14,15</sup> To examine the added value of retinal examination, we studied the prevalence, clinical characteristics, and outcome after diagnosis of patients with suspicion of a HE and retinopathy grade III/IV in the ED in order to distinguish which patients should undergo retinal examination.

## 2 | METHODS

### 2.1 | Patient selection

We conducted a retrospective cohort study of consecutive patients with a suspected HE admitted to the ED of the Flevohospital between 2012 and 2015. The hospital is a medium-sized teaching hospital covering a representative patient population consisting of different ethnicities. Cases were selected using the DBC-codes coding for hypertensive crisis and ICD-codes i10, i15, i16. The DBC coding system is the national coding system used in the Netherlands for reimbursement.

Patients were included according to their BP at time of presentation. Based on international guidelines, patients were included with either a systolic blood pressure (SBP)  $\geq 180$  mm Hg or diastolic blood pressure (DBP)  $\geq 120$  mm Hg. Inpatients who developed hypertension during hospital admission were excluded. BP was measured in a quiet ED room after a 10-15 minutes rest. BP measurements were taken several times over a time period of 15-30 minutes, using an automated, oscillometric device. The lowest values were noted in the patient's file.

Data concerning previous vascular complications, antihypertensive drug use and symptoms and signs at time of presentation were obtained from medical records. Furthermore, we studied the laboratory results, description of EKGs and retinal examination, X-rays and, when available, CT-scans for acute end-organ damage. Patients

were then further classified as having a HE based on the presence of acute end-organ damage.

Microangiopathic hemolysis was defined as thrombocytopenia with either an increased lactate dehydrogenase level or decreased haptoglobin level. Hypertensive encephalopathy was defined as the presence of delirium, loss of consciousness, or convulsions without other cause. Acute renal damage was defined as the presence of dysmorphic erythrocytes in urine in combination with acute (on chronic) renal failure. Retinopathy grade III or IV was present when bilateral cotton wool spots, flame-shaped hemorrhages and/or papilledema were found by means of retinal examination. Acute cardiomyopathy was either ST-elevation myocardial infarction or non-ST-elevation myocardial infarction together with elevated markers troponin and creatininkinase-MB or chest discomfort. Acute pulmonary edema was based on clinical signs and radiological findings.

When there was indistinction about the presence of acute end-organ damage, data were independently reviewed by an objective adjudication team, consisting of an endocrinologist, internist, and ophthalmologist.

### 2.2 | Clinical outcome

By reviewing medical records and discharge letters, treatment according to the guidelines and the outcome after diagnosis and treatment were evaluated. Adverse events during follow-up were classified as patients returning to the hospital with neurological complaints, and/or death within a period of 2 weeks.

### 2.3 | Statistical analysis

Statistical analysis was performed using SPSS version 25 (IBM, The Netherlands). Within each clinical outcome, baseline characteristics of patients were compared. To compare differences between groups on continuous parameters with a normal distribution, Student's *t* test was used. To compare continuous parameters without a normal distribution, Wilcoxon rank-sum test was used. For categorical or dichotomized parameters, proportions between groups were compared using chi-squared test or Fisher's exact test. A *P* value lower than .05 was considered statistically significant.

## 3 | RESULTS

Out of 356 patients consecutively admitted to the ED between January 2012 and December 2015 with a suspected HE, 271 met the BP criteria for inclusion.

Most patients (85.6%) were referred to internal medicine, 4.8% of patients were referred to cardiology and 4.8% to neurology. Headache was the main complaint reported (57.9%), followed by visual disturbances (26.6%), chest pain (14.4%), dyspnea (7.7%), and neurologic deficit (6.6%).

### 3.1 | Clinical characteristics of patients undergoing funduscopy

Funduscopy was performed in less than half of the cases (44.6%; 95%CI 37.1-53.3). These patients were significantly less often known with hypertension, diabetes mellitus, and chronic kidney disease (eGFR < 50 mL/min) were younger and less often used antihypertensive drugs (Table 1). Funduscopy was also more frequently performed when patients reported visual complaints ( $P = .003$ ). Both systolic and diastolic BP were higher in patients who had undergone funduscopy. Seventeen patients had retinopathy grade III or IV (14.0%; 95%CI 8.2-22.5).

### 3.2 | Clinical characteristics of patients with retinopathy

Eighteen patients (6.6%; 95%CI 3.9-10.5) met the criteria for HE. In fourteen of these patients, retinopathy was the only end-organ

**TABLE 1** Characteristics of patients with and without funduscopy

	No funduscopy (N = 150)	Funduscopy (N = 121)	P value
Male	47 (31.3%)	50 (41.3%)	.088
Age	60 (15.1)	51 (12.2)	<.001
Known hypertension	108 (72.0%)	70 (57.9%)	.015
Diabetes mellitus	23 (15.3%)	9 (7.4%)	.045
Cardiovascular disease	32 (21.3%)	21 (17.4%)	.412
Chronic kidney disease	31 (20.7%)	9 (7.4%)	.002
Use of antihypertensive drugs	90 (60.0%)	46 (38.0%)	.001
Headache	80 (53.3%)	77 (63.6%)	.088
Visual disturbances	29 (19.3%)	43 (35.5%)	.003
Neurologic deficit	9 (6.0%)	9 (7.4%)	.637
Chest pain	25 (16.7%)	14 (11.6%)	.235
Dyspnea	7 (4.7%)	14 (11.6%)	.035
Number of antihypertensive drugs	2.3 (1.2)	2.0 (1.0)	.446
Systolic blood pressure emergency department	204 (19.0)	211 (21.0)	.005
Diastolic blood pressure emergency department	105 (21.3)	116 (19.5)	<.001

Note: Data are either presented as numbers with percentages or means with standard deviation.

damage. Among the other four patients, one was diagnosed with hemolysis, acute renal failure, and retinopathy; one with acute cardiomyopathy and pulmonary edema; one had hypertensive encephalopathy and retinopathy and one had acute cardiomyopathy in combination with retinopathy. Prevalence of retinopathy in different BP categories (based on BP at presentation) is shown in Tables 2 and 3. These tables visualize that the prevalence of retinopathy seems to increase with BP. The high prevalence of retinopathy in category SBP < 180 mm Hg (25%) can be explained by the high DBP in the one patient with retinopathy (138 mm Hg) and the small number of patients in this category.

Mean SBP and DBP were significantly higher at time of presentation in patients diagnosed with retinopathy grade III/IV (Table 4). Sex, age, medical history, and use of antihypertensive drugs were equally distributed. Only 6 out of 17 patients with retinopathy reported visual disturbances, which was comparable to the presence of visual complaints in patients without retinopathy ( $P = .982$ ).

### 3.3 | Clinical outcome

Of the 18 patients who met the criteria for HE, 9 were treated with intravenous antihypertensive drugs according to guidelines. The other 9 were treated with oral medication. One of these patients presented with neurologic deficits a couple of hours after taking antihypertensive medication and was diagnosed with ischemic stroke. Among the patients not diagnosed with a HE ( $n = 253$ ), one patient was re-admitted to the ED one day after presentation and diagnosed with subarachnoid hemorrhage.

## 4 | DISCUSSION

According to international guidelines, patients presenting at the ED with a suspected HE, retinal examination should be performed to rule out retinopathy grade III/IV since this requires different treatment. However, in clinical practice funduscopy is poorly performed or hampered by the non-continuous presence of an ophthalmologist.<sup>16</sup> This can lead to treatment delay and incorrect treatment. Identification of patients with retinopathy grade III/IV admitted to the ED with a suspected HE can facilitate the selection of patients in need of controlled BP lowering with intravenous medication.

The present study shows that retinopathy grade III/IV affects one in seven examined patients in the emergency care setting. The only factor that accounts for a higher risk of retinopathy is BP. The BP criteria stated in the Dutch guideline on when to suspect a HE are higher (SBP  $\geq$  200 mm Hg or DBP  $\geq$  120 mm Hg) than those in international guidelines.<sup>17</sup> We found that some patients not meeting the Dutch BP criteria did have retinopathy. Comorbidities and presenting complaints did not differ between patients with and without retinopathy. Visual disturbances were only present in one third of the patients with retinopathy which is comparable to results found in previous studies.<sup>14,18</sup> This indicates that anamnesis alone is not sufficient

**TABLE 2** Prevalence of retinopathy according to different groups of systolic blood pressure

	SBP < 180 mm Hg (n = 4)	SBP ≥ 180, <200 mm Hg (n = 101)	SBP ≥ 200, <220 mm Hg (n = 97)	SBP ≥ 220 mm Hg (n = 69)
Retinopathy	1 <sup>a</sup> (25%)	2 (2%)	3 (3.1%)	11 (15.9%)

Note: Abbreviation: SBP: systolic blood pressure.

<sup>a</sup>Diastolic blood pressure in this patient was 138 mm Hg.

**TABLE 3** Prevalence of retinopathy according to different groups of diastolic blood pressure

	DBP < 110 mm Hg (n = 129)	DBP ≥ 110, <120 mm Hg (n = 57)	DBP ≥ 120, <130 mm Hg (n = 40)	DBP ≥ 130 mm Hg (n = 45)
Retinopathy	2 (1.6%)	5 (8.8%)	2 (5%)	8 (17.8%)

Note: Abbreviation: DBP: diastolic blood pressure.

**TABLE 4** Characteristics of patients with and without retinopathy

	No retinopathy (N = 104)	Retinopathy (N = 17)	P value
Male	42 (40.4%)	8 (47.1%)	.604
Age	51 (12.3)	50 (12.0)	.128
Known hypertension	61 (58.7%)	9 (52.9%)	.658
Diabetes mellitus	9 (8.7%)	0	.357
Cardiovascular disease	20 (19.2%)	1 (5.8%)	.301
Chronic renal disease	9 (8.7%)	0 (0%)	.357
Use of antihypertensive drugs	40 (38.5%)	6 (35.3%)	.803
Headache	68 (65.4%)	9 (52.9%)	.323
Visual disturbances	37 (35.6%)	6 (35.3%)	.982
Neurologic deficits	8 (7.7%)	1 (5.8%)	1.000
Chest pain	13 (12.5%)	1 (5.8%)	.689
Dyspnea	12 (11.5%)	2 (11.7%)	1.000
Number of antihypertensive drugs	2 (1.0)	2 (0.8)	.099
Systolic blood pressure emergency department	209 (19.8)	223 (24.4)	.001
Diastolic blood pressure emergency department	115 (19.7)	125 (15.9)	.001

Note: Data are either presented as numbers with percentages or means with standard deviation.

to rule out retinopathy. We also did not find an association between symptoms of hypertensive encephalopathy and retinopathy, stated in previous studies as being a predictor of retinopathy grade III/IV.<sup>19</sup>

This could be due to the fact that patients with extensively risen BP are early admitted to the ED, preventing encephalopathy to develop.

We found that SBP and DBP at time of presentation were significantly higher in patients with retinopathy. However, we also found that two patients diagnosed with retinopathy did not meet the BP threshold stated in the Dutch guideline. This could be due to the fact that these patients had a markedly elevation in BP relative to their normal BP. It is known that a sudden increase of BP can also lead to retinopathy grade III/IV, even if SBP is below 200 mm Hg and DBP below 120 mm Hg.<sup>17</sup> In the FOTO-ED study, retinopathy grade III/IV was found at SBP levels ≥ 170 mm Hg and DBP levels ≥ 90 mm Hg.<sup>20</sup>

In normotensive subjects, cerebral autoregulation secures the maintenance of a constant blood flow by cerebral vasoconstriction. At a mean arterial pressure of > 140-180 mm Hg, this compensating capability is diminished. It is thought that the presence of retinopathy grade III/IV reflects cerebral hyperperfusion and therefore indicates compromised cerebral auto-regulatory capacity.<sup>4,8</sup> Lowering the BP should therefore be done with intravenous antihypertensive drugs under strict control. In our study, we found that one patient who was diagnosed with retinopathy grade III and treated with oral antihypertensive drugs, developed ischemic stroke after taking medication, probably due to an uncontrolled lowering of BP. This event supports the guidelines' recommendation that reduction of mean arterial pressure should be no more than 20%-25% within a period of minutes to 2 hours to prevent hypoperfusion.<sup>21</sup>

Retinal examination was performed in 44.6% of patients. This number is comparable to other studies.<sup>22,23</sup> It is thought that patients with long-standing hypertension are protected from cerebral hyperperfusion at higher BP levels.<sup>20</sup> This selection of patients, with overall less comorbidities and of younger age, may have occurred because the treating physician did consider the presence of retinopathy in these patients more likely. This selection bias may either under- or overestimate the prevalence of retinopathy.

In contrast to other studies, we found a low prevalence of acute cardiomyopathy, hemolysis, renal insufficiency, and encephalopathy.<sup>18,24</sup> This can be partly explained by the small study population.

Furthermore, patients referred to the neurologist and cardiologist with neurologic deficits, chest pain, or dyspnea may not have been recognized as having a HE.

This study has its limitations, mainly inherent in the retrospective aspect. Because not all patients underwent retinal examination and patient characteristics were not equally distributed, a prevalence of retinopathy cannot be determined with certainty. Besides, by also including patients with BP values below the set values in the Dutch guideline, we may have included patients in our study who were not considered as having a HE by the treating clinician at the time they were examined at the ED. This may have led to less funduscopies and therefore an underestimation of the prevalence of retinopathy. However, we do not think this has influenced the study outcome since the risk of having grade III/IV retinopathy is highest in patients with the highest BP.

It would be interesting to have more detail on the severity of pre-existing hypertension such as left ventricle mass, proteinuria, and types of used antihypertensive drugs. Due to the retrospective design, these data were not available. However, we do not believe this has influenced our study outcome since the analysis focuses on acute organ damage in patients presenting at the ED.

Despite its retrospective design, this is the first study with consecutive patients to provide an estimate of the prevalence of grade III/IV retinopathy and to investigate which characteristics correlate with its presence.

In conclusion, our study shows that the prevalence of retinopathy grade III/IV is high among examined patients. Except for higher mean SBP and DBP among patients with retinopathy, we found no clinical signs or symptoms that are associated with the presence of retinopathy grade III/IV. Since retinopathy grade III/IV cannot be ruled out safely, we state that retinal examination should be performed in every patient regardless of logistic boundaries. Consequently, funduscopy should become readily accessible in every ED. The occurrence of ischemic stroke in one patient with retinopathy who was not properly treated endorses this.

#### CONFLICT OF INTEREST

Charlotte M. Nijskens: None. Saskia R. Veldkamp: None. Dymph J. van der Werf: None. Arnold H. Boonstra: None. Marije Ten Wolde: None.

#### AUTHOR CONTRIBUTIONS

C Nijskens involved in data collection, data analysis and interpretation, primary author. S Veldkamp involved in data collection and critical revision of the manuscript. D van der Werf involved in critical revision of the manuscript. A Boonstra involved in critical revision of the manuscript. M Ten Wolde involved in data analysis and interpretation, critical revision of the manuscript, and principal investigator.

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