Hypertension and Sequelae in Individuals with Thalidomide Embryopathy and Dysmelia

Recommendations for Diagnosis, Prevention, and Treatment

September
2017

SCHÖN HELFEN
CONTERGAN SPRECHSTUNDE HAMBURG
Schön Klinik Stiftung für Gesundheit

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Published by:

Schön Klinik Stiftung für Gesundheit gemeinnützige GmbH
Managing Director: Dr. Anne-Marie Hamm
Seestr. 5 a, 83209 Prien am Chiemsee

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Hamburg, 24. May 2018

Acknowledgements

In October 2016, Schön Klinik Stiftung für Gesundheit hosted a conference of experts on “Hypertension in Individuals with Thalidomide Embryopathy.” This article is a summary of the individual presentations and discussions.

On behalf of the Schön Klinik Stiftung für Gesundheit, I would like to thank the following persons for their presentations:

Prof. Dr.-Ing. Klaus Affeld

Univ. Prof. Dr. med. Cor de Wit

Dr. med. Amir Kapic

Dipl.-Ing. Christoph Lederer

Priv.-Doz. Dr. med. Stephan Lüders

Priv.-Doz. Dr. med. Tobias N. Meyer

Dr.-Ing. Sarah Schneider

Dr. med. Jan Schulte-Hillen

Dr. med. Julius Weinrich

Prof. Dr. med. Burkhard Weisser

The fact that experts of many different fields took part in an interdisciplinary dialogue and participated actively in the discussion deserves special mention. I would especially like to thank Dr. med. Jan Schulte-Hillen, who was the first to systematically address this topic, thus laying the groundwork for this dialogue. I would also like to thank Ms. Dehlia Brkitsch and Dr. Anne-Marie Hamm, who were instrumental in arranging this conference.

Rudolf Beyer

Introduction

For several years, there have been clear indications that individuals with thalidomide embryopathy are at a comparatively higher risk for hypertension and the resulting diseases[1].

The affected individuals (born between 1958 and 1963) are now at an age at which an increase in cardiovascular diseases can generally be expected. At the same time, several factors make their participation in preventive healthcare, a key component of the healthcare system, more difficult. One example of this is the method of measuring blood pressure using a cuff on the upper arm and a manometer. In individuals with short arms, this basic diagnostic test cannot be reliably implemented.

There is probably no other parameter in medicine that can be so easily measured while also having such a large effect on diagnostics and treatment planning. And globally, arterial hypertension is the most important risk factor for mortality and morbidity.

Measuring blood pressure in patients with thalidomide embryopathy and dysmelia

Measuring blood pressure is an integral part of preventive medicine. Self-monitoring by patients at home is especially important because these values are less likely to be affected by situational distortion.

However, the usual method of measuring blood pressure is not possible in patients with thalidomide embryopathy and dysmelia (malformation of the limbs) because the basic prerequisites are not sufficiently met. The limb malformations are also usually associated with vascular malformations (hypoplastic arteries)[2]. This could be another factor that distorts blood pressure measurements at the upper arm.

Around 87.8% of all patients with thalidomide damage have malformations of the upper limbs. The degree of these malformations varies widely. Around 10.5% of patients have no arms; the hands are attached directly to the shoulders (phocomelia). The limb is completely missing (amelia) in around 5.0%[3].

Affected anatomical regions	Percentage of Thalidomiders
Upper limb in generall (all defects)	87.8%
- Individuals with Phocomelia* of the upper limb in this group	10.5%
- Individuals with Amelia** of the upper limb in this group	5.0%
Lower limb in general (all defects)	53.0%
- Individuals with Phocomelia/Amelia of the lower limb in this group	1.8%
Spine and pelvis	55.6%
Head and sensory organ defect	35.4%
Deafness	5.4%
Impaired vision or blindness	35.1%
Internal organs (incl. heart, kidneys, gastrointestinal tract)	38.4%

* Arms/legs are not formed, the hands are attached at the shoulder, the legs at the hips.
** Arms and legs are not formed, hands and feet are missing.

Table 1: Overview of prenatal damage of the different areas of the body (modified from[3]). Percentage is not cummulative, sum exceeds 100% because multiple anatomical regions may be affected in an individual) and because overall anatomical regions are shown together with detailed regions (e.g. Amelia is also represented in the "upper Limb)

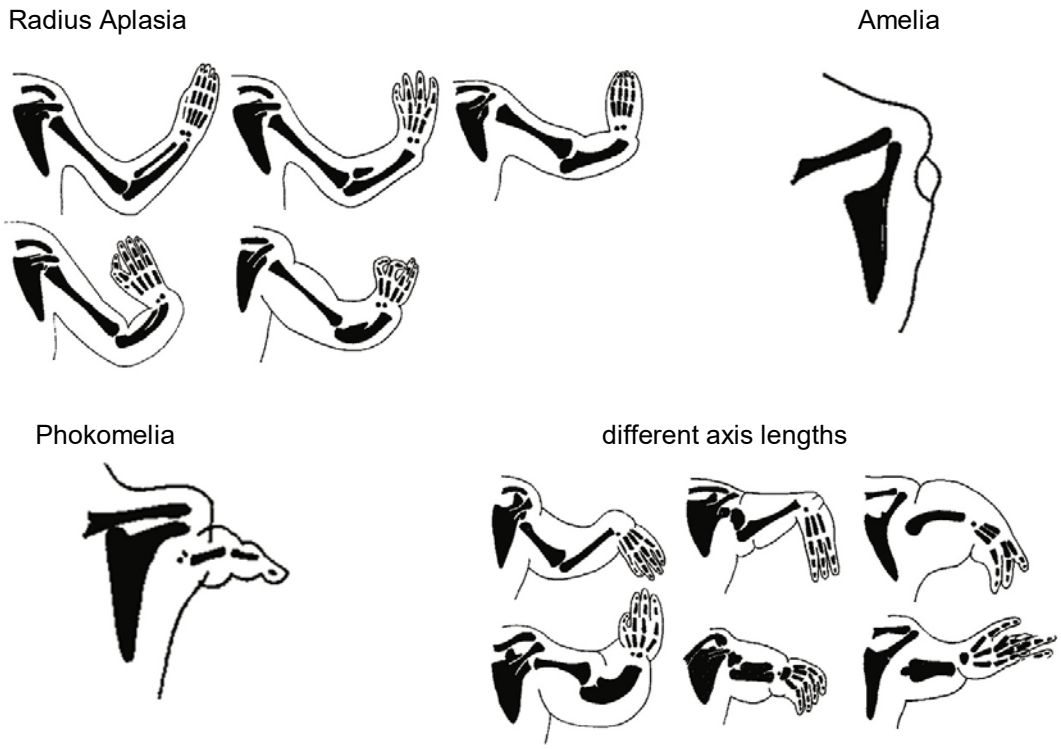

Figure 1: Variability of the malformations of the upper limb in thalidomide embryopathy modified from[4])

Prevalence of hypertension in individuals with thalidomide embryopathy

A Japanese study[1] with 76 individuals with thalidomide embryopathy found that 46.7% of them had high blood pressure. In comparison, the prevalence of hypertension in the age group from 50 to 59 years is 31.8%[5]. Although the direct comparison is not valid evidence due to the small number of cases, it is at least an indication of the significantly higher occurrence of high blood pressure in individuals with thalidomide embryopathy.

A Brazilian study with 28 individuals showed that the early onset of cardiovascular diseases occurs significantly more frequently than in the general population[6].

The reasons for the greater prevalence of high blood pressure in individuals with thalidomide damage could be a comparatively poorer health-related quality of life and the high prevalence of mental disorders[7].

In addition, it is assumed that some of the persons affected by thalidomide have poorer access to health care due to real barriers[8, 9], social withdrawal, or avoidance of physicians. This is a potential disadvantage for the affected persons, because considerably more persons develop hypertension after reaching their mid-50s[5].

Whether there are additional factors that can lead to hypertension in individuals with thalidomide embryopathy or dysmelia is not currently known. However, in a comparison group, namely persons with amputated limbs, the mortality from cardiovascular diseases is high[10]. This is attributed in part to difficult-to-treat hypertension.

Conclusion

1. In persons with thalidomide embryopathy and dysmelia, there are considerable problems involved in the reliable measurement of blood pressure.

2. The usual methods of preventive medicine are inadequate.

3. Various factors probably lead to a higher occurrence of undiagnosed hypertension and secondary diseases.

Recommendation for blood pressure diagnostics in thalidomide embryopathy and dysmelia patients

1. For patients with a defect of the upper arm, a comparative blood pressure measurement should be taken at all four limbs if possible. If the pressure measured at the legs is considerably higher than that measured at the arms (>20 mmHg), the measurements should preferably be made at the legs in the future.

2. During scheduled surgical procedures, conducting comparative blood pressure measurement using invasive intra-arterial or conventional methods in order to determine an individual corrective factor could be considered. In this case, the indication, the benefit, and the risks must always be weighed[11] (secondary bleeding, hematoma, pseudoaneurysm, arteriovenous fistula, vascular spasm, ischemia with loss of the limb, infection, unintentional intra-arterial injection)[12].

3. Regardless of the blood pressure measurement, a specific search for damage to end organs (signs of secondary hypertension) and risk factors should be conducted in all individuals with thalidomide embryopathy or dysmelia. The following examinations are recommended:

    - Laboratory blood tests: lipids, cholesterol, glucose, uric acid, cystatin C, electrolytes
    - Laboratory urine tests: protein
    - Electrocardiography
    - Echocardiography
    - Duplex ultrasound of the arteries supplying the brain
    - Duplex ultrasound of the abdominal aorta and the pelvic and leg arteries
    - 24-h blood pressure monitoring to register the day-night pattern (dipping)
    - Measurement of pulse wave velocity
    - Ophthalmoscopy: fundus hypertonicus

Taking blood samples is a regular challenge in people with thalidomide embryopathie and Dysmelia.

- Plane enough time for the procedure
- Have the most experienced staff
- Use a transdermal local anaesthetic e.g. EMLA anaesthetic cream
- Provide something for warming the extremities like a warm water compress or a washtub with warm water. Try the temperature first to prevent scald.

Methods of blood pressure diagnostics

If it is impossible to measure blood pressure conventionally at the upper arm because the arms are missing or too short, the legs can be used for measuring blood pressure.

In a study[13] with 960 healthy subjects of different age groups, systolic blood pressure was an average of 18 mmHg higher when measured at the ankle.

A Japanese working group compared the different blood pressures at the leg and arm (ankle-brachial index) in 17 patients with thalidomide embryopathy with existing data from large US studies[14]. The data from this comparison led to the following recommendation:

When measuring blood pressure at the lower limb, an oscillometric blood pressure device should be used and the index marking of the cuff should be in the region of the posterior tibial artery (inner ankle). The cuff must be adjusted to the circumference of the ankle. The blood pressure should be measured with the patient lying down. The following formula can be applied to correct the results:

$$\textit{Blood pressure}_{syst}\ [mmHg] = \textit{Blood pressure}_{syst}\ [mmHg]\ \textit{of the lower limb} \times 0.88$$

If a cuff size M was used, the value was 8 mmHg lower than for cuff size S. Thus, if cuff size M is applied, the following formula should be used:

$$\textit{Blood pressure}_{syst}\ [mmHg] = \textit{Blood pressure}_{syst}\ [mmHg]\ \textit{of the lower limb} + 8\ [mmHg] \times 0.88$$

Example when using cuff size M:

Blood pressure of the lower limb 160/90 mmHg
$$\textit{Blood pressure}_{syst} = (160\ mmHg + 8\ mmHg) \times 0.88 = 147.8\ mmHg$$

This correction factor is approximately equivalent to the assumed normal ankle-brachial index (ABI 0.9)[15].

Important conditions for interpreting the blood pressures measured in this way are the exclusion of peripheral arterial occlusive disease (false low blood pressures due to vascular constriction) and Mönckeberg's media sclerosis (false high blood pressures due to stiffness of the vascular wall). To evaluate the blood pressures measured at the lower limb, a Duplex or Doppler ultrasound of the arteries of the legs should first be made.

An ill-fitting blood pressure cuff is the most common source of a faulty blood pressure measurement[16]; the cuff size should therefore be selected to fit the measured average circumference above the ankle where the cuff is applied.

Measurements at the thigh are generally possible only with blood pressure monitors used in anesthesiology and intensive medicine, as the devices usually used in practices or at home do not generate enough cuff pressure. In addition,

measurement at the calf and thigh is extremely painful and therefore not suitable for long-term monitoring.

A limitation of measuring blood pressure at the legs is that the accuracy is not comparable with measurements at the upper arm[17]. When assessing blood pressure, signs of secondary hypertension and end organ damage should always be taken into consideration as well.

There are newer blood pressure devices (SomnoTouch™, Somno Medics or ClearSight™, Edwards Lifesciences), that allow blood pressure to be measured on fingers, making them theoretically suitable for individuals with dysmelia. A case description showed the successful use during perioperative monitoring of a person with thalidomide-induced phocomelia[18].

The measurement principles used are the Peñáz method[19] with the ClearSight™ system and the pulse transit time (PTT) with SomnoTouch™[20].

Both devices require a conventional blood pressure measurement for individual calibration and are not validated for measurements at the lower limbs. Because the SomnoTouch™ determines blood pressure using pulse transit time, the patient's height assuming a normal arm length is used in the algorithm. This limits the ease of use in persons with dysmelia.

The ClearSight™ system is designed as a monitor for intensive medicine and its high cost makes it less suitable for routine operation in a primary care practice.

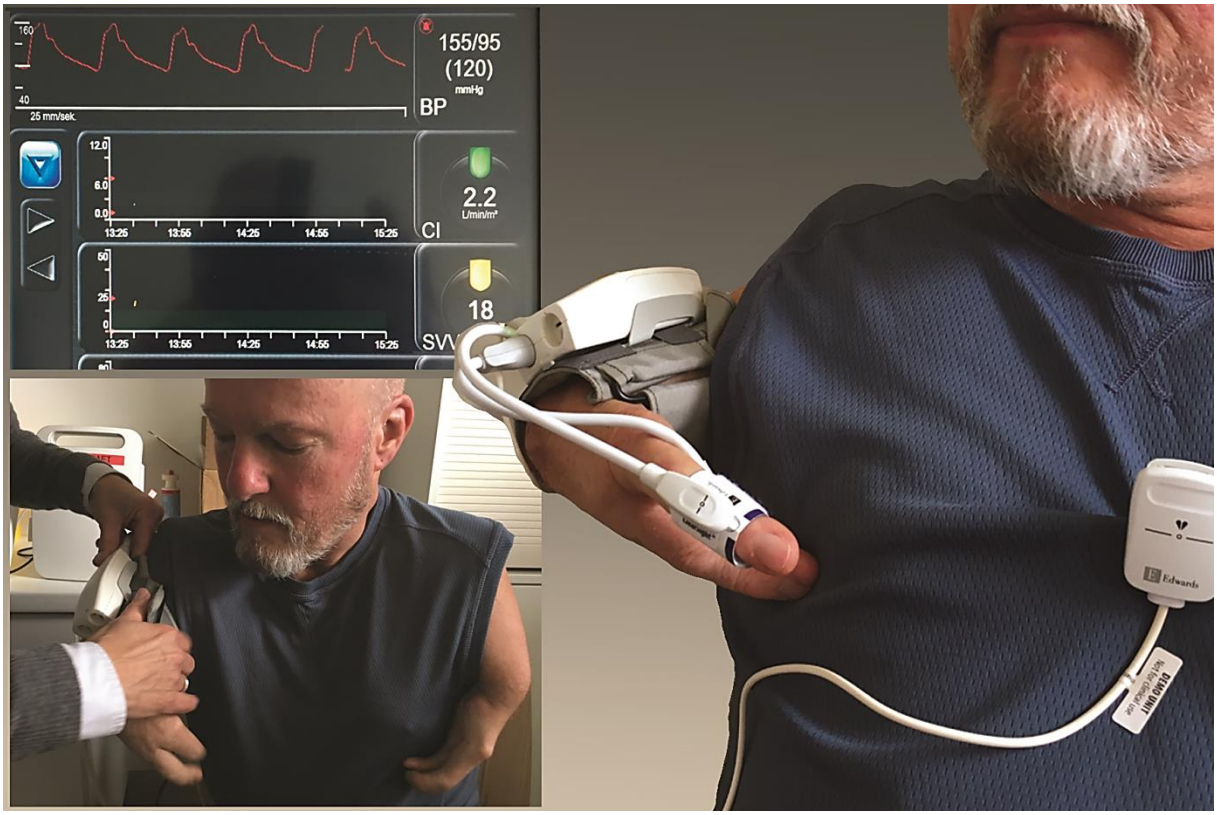

Figure 2: Edward Lifesciences ClearSight™ system with dysmelia of the upper limb

The working group headed by Prof. Dr.-Ing. K. Affeld, Charité - Universitätsmedizin Berlin, Laboratory for Biofluid Mechanics in Berlin, has developed a new method for noninvasive blood pressure measurement at the cheek (pressure of the facial artery)[21]. The measurements are based on a photoplethysmographic method. The method is not yet in use because the measurement algorithm on which it is based has not been sufficiently validated. As measurement is conducted independently of the limbs, this method would be very suitable for all individuals with dysmelia.

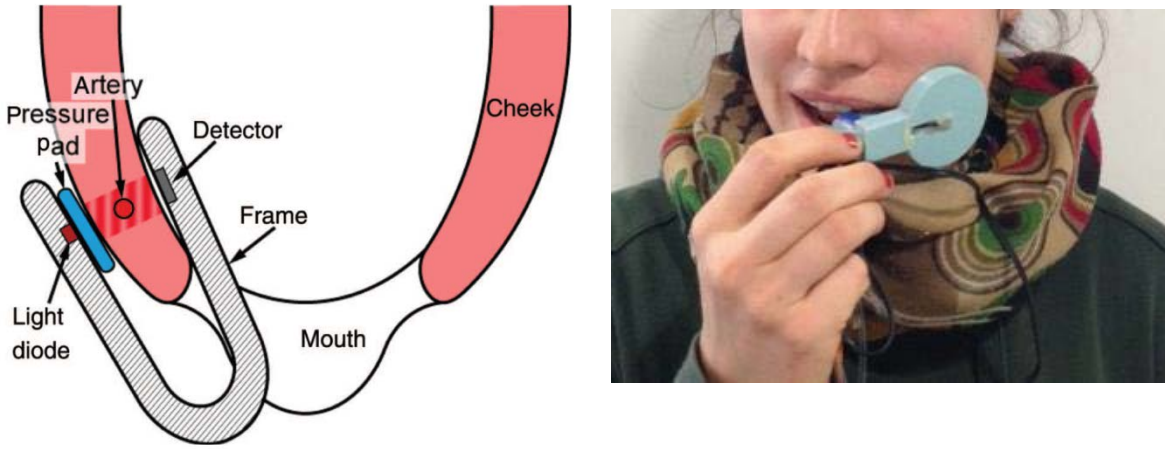

Figure 3: In the testing phase – noninvasive method for measuring blood pressure at the cheek. Schematic of the measurement device. A light diode, a light detector, and the pressure pad are mounted on a frame which is placed in the corner of the mouth.

It is useful to conduct 24-hour blood pressure monitoring because an impaired day-night rhythm can be an additional indication of hypertension[22]. Newer devices for 24-hour blood pressure monitoring for outpatients can also measure the pulse transit time to determine vascular stiffness. Vascular stiffness is another criterion for the indirect diagnosis of hypertension[23, 24].

Home measurement is important for the treatment of hypertension. For patients with dysmelia, blood pressure devices should preferably be selected on a case-by-case basis according to their ease of use, ideally allowing them to be used without assistance. It may be possible to have a conventional device modified by a technician. It would be useful to check the correct measuring method and fluctuations in measurements of the devices individually by measuring blood pressure on the lower leg in the primary care practice.

Treatment of hypertension

Because there are no independent studies or data with respect to the optimal blood pressure for persons with thalidomide birth defects, the recommendations of the German Hypertension League are applied unconditionally to this patient group.

Recommendation for	Target blood pressure		
General	syst./diast.	below	140/90 mmHg
Diabetes	diastolic	from	80-85 mmHg
Biological age > 80 years	systolic	from	140-150 mmHg
Nephropathy with proteinuria (≥ 300 mg/d)	systolic	below	130 mmHg

Table 2: Recommendations of 2016 for blood pressure levels

General measures

General measures can effectively influence systolic blood pressure[25] and should always be part of treatment.

Measure	Reduction of systolic pressure
Reduction of salt	2-8 mmHg
Reduction of alcohol consumption	2-4 mmHg
Exercise	4-20 mmHg
DASH (Dietary Approaches to Stop Hypertension)	8-14 mmHg
10 kg weight loss	5-20 mmHg
3-week laugh training / relaxation measures	6 mmHg

Table 3: General measures for lowering blood pressure

Drug therapy

The currently standard substance classes are also suitable for drug therapy of patients with thalidomide defects. Adherence is very important[26, 27]. Patients will accept long-term treatment only if they have understandable information on the anticipated effect and possible side effects.

This applies in particular to persons with thalidomide defects, because in general, their experience has made them extremely skeptical and cautious in their use of drugs. In addition to appropriate attention to treatment, methods of digital medicine may have a positive effect.

One unsolved problem in treatment is how to control blood pressure with antihypertensive agents in patient with clear signs of hypertension but no way of monitoring blood pressure. This can be the case, for example, in individuals in whom four limbs are affected.

A meta-analysis in 2015 showed that sustained orthostatic hypotension is associated with a significantly increased risk of coronary heart disease, heart failure, stroke, or death[28]. The adverse side effect of antihypertensive agents is considered to be one of the most common causes of orthostatic hypotension[29].

Because these risks must be classified as just as serious as the risk of hypertension, “blind” drug treatment is not a suitable solution.

An attempt must be made to determine valid blood pressure levels in these patients on a case-by-case basis under clinical conditions. If at least one finger is present, this can be done using the ClearSight™ system and comparative invasive measurement of blood pressure.

Prevention of hypertension and sequelae through exercise

There are increasing indications of a higher cardiovascular risk in persons with thalidomide embryopathy. In addition, there is a higher probability that this group will get less exercise due to their disability. At the same time, it is known that persons who are not physically fit benefit in particular from an increase in physical activity. Physical fitness has a crucial effect on morbidity and mortality[30].

For the question as to how physical fitness can be assessed in patients, self-assessment (Borg scale)[31] by patients has been proven to be a simple, yet valid method.

Due to the huge differences in the extent of impairment in persons with thalidomide defects, no generally valid recommendations can be given for a suitable sport. The suitable types of regular physical activity must be determined for each individual. Sports therapists and personal trainers can play a key role in this determination.

A number of studies have shown that an immediate effect of training can be achieved even with very simple means[32]. Physical activity can be increased significantly with specific exercise recommendations (for example: 10,000 steps a day) for daily routine and by using a pedometer. This can contribute to a relevant reduction of the risk profile for cardiovascular diseases[33].

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