

THERAPEUTIC TRIAL  
**CAPILLARY RESISTANCE IN GERIATRY**  
**A STUDY OF A MICROANGIOPROTECTOR = ENDOTELON**

Even though our knowledge of capillaries goes back quite some time it is only in the last thirty years that we've seen any real development. There are numerous studies on arteries and veins reports on microcirculation really only started to be seen in the last 6 or 7 years, especially in France from Cloarec and Larenn and their collaborators.

The capillaries distribute blood to the cells, assuring exchanges between the blood and tissue. The rest of the circulatory system is just the way of assuring these exchanges.

It is logical therefore to anticipate the importance there is in conserving all of the integrity of the microcirculation and in the case of problems having a battery of therapeutic agents available capable of fixing the problems. Endotelon is just such a medication.

Recent works on the anatomy and physiology of the microcirculation allows us to better understand how all the elements of the terminal network react. As was pointed out by Merlen, we must never confuse microcirculation with capillaries, the latter being just the last element in the terminal network.

If it appears that only the physiological variations of the capillary circulation are complex and infinite, the pathological disturbances are no less rich in their different aspects.

Permeability and resistance can be modified by altering the structure of the capillary, changes in the composition of the plasma, hemodynamic disturbances or in the freeing of the chemical transmitters under the influence of diverse therapies, outside aggressions, etc.

While vascular resistance decreases we speak of capillary frailness which is a pathological state capable of being identified by the appearance of purpura. The hemastase being at first vasculo-plaquetair, we can distinguish thrombopenic and vascular purpura, which are both capable of coexisting together. Among the purpura from a vascular origin we can list: those of capillary infection (meningococcus, staphylococcus, streptococcus, pneumococcus, and negative Gram bacilli. Those attained from vascular of an inflammatory nature (rhumatoid purpura of Schoenlein-Henoch, purpura hyperglobulin, and senile purpura of Bateman. Those from metabolic diseases or diverse affections (diabetic microangiopathy, HTA, hepatitis, cirrhosis, renal affections). Those from isolated constitutional capillary fragility almost exclusively feminine, fragility from scurvy, Rendu-Osler disease or genetic angiomatosis.

Beyond the senile purpura of Bateman advanced age is not of itself a factor in capillary fragility.

The systematic exploration of capillary resistance using Parrot's angiosterrrometer used on all of the subjects in this study older than 60 allowed us to get a certain number of points that will be the subject of a complete analysis in a later article that will be dedicated to this subject: A significant increase in capillary resistance in people older than 70 only in the absence of all pathological alteration. It was higher in women and higher at night than during the day. It decreased in those with hypertension and diabetes. It was lowered in those who were bedridden.

As for the capillary permeability that was not explored systematically (Landis test) the numbers for an adult should be a little higher in older people.

#### I. THE PRODUCT USED

Our clinical study was carried out in the interest of geriatrics using the microangioprotector Endotelon. It is made up of procyanidolic oligomer extracts from the woody tissue of grapes (Alasquelier). The tannin of the grape will result in a more or less large polymerization of an

elementary molecule belonging to the class leucoanthocyanes, answering to the structure of a flavanol, the tetrahydron 5,7,3,4, flavanoid product 3.4 of which the synthetic version was developed in 1968 (J. Michaud, J. Masquelier) but which shows itself to be unstable under normal conditions under the form leucocyanidol comprised of a molecule of catechine associated with a molecule of leucocyanidol. In plants this dimere is found to be linked to a whole host of neighboring structures that we group under the name of procyanidolic oligomers. The progress resides in the extraction progress that allows us to obtain the stable forms due to the high vitamin P activity. The weight of the oligomers must be sufficiently low enough in order to avoid all risk of toxicity particularly catabolistic hepatitis but high enough to expand their affinity vis-à-vis the proteins.

The toxicological study (Laparra) done on mice suggests intense toxicity when taken orally DL<sub>50</sub> of 3.1 g/kg.

In guinea pigs the elevation of the capillary resistance is important, reaching a maximum at the end of 24 hours. In a rat this action is persistent 4 days after one oral dose. An important lowering of the capillary permeability was found in a rabbit.

The autodiographic study of the localization of marked T.H.F.D. in a mouse (tetra-hydroxy-flavandiol 14 C) demonstrates its binding at the level of mucopolysaccharides and was in favor of the pharmacological action in the capillaries, constituting primarily of mucopolysaccharides (J. Laparra, J. Michaud, M<sup>lle</sup> M.F. Losca, P. Blanquet, J. Masquelier).

Most recently J. Masquelier, J. Michaud, J. Laparra and M<sup>lle</sup> M.C. Dumon underlined the necessity of a classification of the derivatives of flavone 3 and they gave it the name Pycnogenols (catechines and OPC). The chemical and pharmacological autonomy of the latter now permits us two groups of natural products: flavone, flavanols, and chalcones that when taken orally in animals and humans is nothing or negligible. The pyenogenol (catechine and OPC) are characterized by their bioavailability.

The product given to us under the name of Endotelon was studied for it's therapeutic activity on patients in the geriatric ward. It was given to us in the form of gastro-resistant pills of 50-mg doses of the active ingredient. It was administered orally 2 or 3 times a day at meal time.

## I STUDY METHODS AND RESULTS

Our clinical study was carried out on patients whose capillary resistance was well below that of normal and who showed at least 5 skin abrasions and a neighboring depression of -20cm of Hg.

The product was only given to those subjects who were in fairly satisfactory health who were not under any therapy or any vascular therapy. They underwent a clinical and biological exam before and after the treatment. It should be noted that none of the subjects did necessarily show clinical signs of capillary fragility. If they did show signs came from the lower limbs, Bateman purpura, telangiectasies and sometimes spontaneous ecchymosis or from contact.

This study was comprised of two parts: One clinical study on the effects of Endotelon and a controlled test using the double-blind method using Endotelon and a placebo.

### 1. Clinical Study of the effects of Endotelon

This was carried out on 46 subjects showing signs of capillary resistance of the Parrot angiosterrrometer. There were 13 men and 33 women with 3 sick between the ages of 50 and 60, 17 between the ages of 61 and 70, 17 between the ages of 71 and 80 and 9 between 81 and 90.

The capillary fragility of these subjects was integrated in 9 different pathological contexts: 9 displayed old arterial hypertension, 5 with a hemiplegie with old arterial hypertension, 7 were diabetics, 10 had a hemiplgie and the others had older problems. For 4 patients only the lowering of capillary resistance could not be attributed to any pathological context.

The initial dose was 100mg a day (one pill in the morning and one at night at mealtime). Later on this posology was altered for some of the patients. This went on for 30 to 45 days depending upon the patient.

The clinical surveillance was constant on what was concerned about the objective and subjective criteria. The biological surveillance before and after the treatment was composed of urine analysis (albumin, sugar, acetone), a control of glycemin, azotemie, protidemie, alkaline phosphatasemie, transaminos SGOT and SGPT, the rate of prothrombin and mes(*unreadable*). The rate of the platelets did not figure into the systematic control, the experiment having shown the absence of the rapport the number of platelets and the values of capillary resistance. Bleeding time, measured in some patients was longer each time there was capillary fragility and vice versa. Finally, in 18 patients a Landis test was done at the beginning and at the end of the treatment.

The efficiency of the Endotelon treatment *on the clinical plan* showed itself by a remarkably rapid disappearance of the ecchymosis where they had existed and the difficulty of their constitution after some days of treatment.

On the *angiosterrometric plan* according the values of the capillary reistance given by the depression in mercury centimeters sufficient enough to provoke the appearance of 3 splotches of broken blood vessels in the studied zone.

We grouped the results into four categories: **Very Good Results**: Capillary resistance higher than 30cm of Hg after treatment. **Good Results**: Capillary resistance in the neighborhood of 30cm of Hg. **Average Results**: Capillary resistance equal to or less than 25cm of Hg and finally **No Results**: No improvement.

Out of the 46 patients we obtained the following results:

Table One – Results

	Very Good	Good	Average	No
Nr of Cases	31	8	6	1
Percentage	67%	17%	13%	2%

Table Two

Average Value of Capillary Resistance at the Beginning and End of Treatment

Beginning	End	1 month after stopping treatment
19	29	25

The *capillary permeability* was studied in 18 patients before and after treatment using the Landis. The average of the water leak before treatment was 16.1 and 9.3 after treatment. This indicates an improvement of 58%. The results were positive for all patients. In referring to the normal figures by A.J. Meyer (water =  $12.2 \pm 2\%$ ) we see that before the treatment the water leak was better than normal in 11 cases, and after treatment in only two cases. The number of the leak values superior to the norm before treatment increases as a function of age (2 out of 7 in the 60 to 70 years old, 2 out of 2 over 80 years old). The average of the protein leak before treatment was 1.04, a very high number when compared to the norms of A.J. Meyer and Landis. The age of our subjects certainly plays a big role. After treatment we obtained in each case a decrease in the protein leak, the average being 0.42. Finally, the average of the capillary filtrates goes from 6.4 before treatment to 4 after treatment.

*The tolerance* of Endotelon was excellent in the quasi totality of the cases. In only one case we noticed on the 10<sup>th</sup> day a coetaneous reaction that was very pruriginous and went away as soon as we stopped the treatment. We noticed no biological problems. The product does not give rise to any habit-forming phenomenon even after 6 weeks.

## **1. Controlled Trial of the Efficiency of Endotelon Using the Double Blind Method**

Two types of coated pills were used, one containing Endotelon and the other a placebo that exactly resembled the Endotelon that were kept in two lots labeled A and B, the identities being revealed after the test. Each jar containing 30 pills allowed us two successive treatments of 15 days using 2 pills a day. One treatment immediately followed the other.

The treatment was carried out on 37 hospitalized patients (9 men and 28 women). Their ages went from 42 to 92 years old (the 6 people younger than 60 were assimilated into our study with the older ones but were dependent and deficient). The average age was 74.7 years old. All the subjects displayed an abnormal angiosterrometry before treatment except for 8 who only displayed 5 or 10 red skin blotches at 30cm Hg. Clinically only 9 patients showed signs of capillary fragility visible as ecchymosis or red skin blotches. 2 of them had a normal angiosterrometry at the beginning. All the patients had an angiosterrometry measure done before beginning treatment, at the end of the first treatment (except for 4) and at the end of the second treatment.

For the most part there existed a polymorbidity in one bedridden state 13 times and in a diabetic 4 times.

Even though there were less improved cases than not it must be taken into account that in 6 of the cases there was normal capillary resistance before the treatment started. All totaled, Endotelon proved to be most certainly effective in 10 out of 21 cases whereas the placebo showed improvement in 3 out of 12 cases. It would appear therefore that Endotelon has a beneficial impact on capillary fragility clearly superior in number and quality than did the placebo.

### **III COMMENTARIES**

The study of a microangioprotector must take into account on one hand the complexity at the same time physiological and physiopathological relative to the microcirculation and the difficulties in approaching this phenomenon in a study like this. On the other hand the action mode that is misunderstood is the complex vitamin P, especially the flavanoid. Among these latter substances the leucoanthocyanes, from which Endotelon comes, appears to have a privileged activity. The study of the therapeutic activity of the latter in humans seemed to us to apply itself on the two better known easiest to apply tests: The angiosterrometry with the aid of the Parrot apparatus for determining resistance and the Landis test for permeability. Taking into account their weaknesses and their limits we were able to put together a methodology as rigorous as possible allowing us to bring into evidence at the same time the anomalies in the studied population and the therapeutic effects of a substance targeted to suppress them.

A preliminary study had as a goal to study the particularities found in the elderly who at first glance have no capillary pathology. This allowed us to put into evidence a relative raising of capillary resistance that comes with age in relation with the adult subjects and a decrease of capillary permeability. To attempt to explain these characteristics we can advance several hypotheses: Decrease in suppleness and caliber of the arterial conduits, the loss of elasticity of the tissue covering the capillaries. All these elements bring along the necessity to increase the necessary depression in order to bring about rupture in the capillaries or in the veins. The qualitative modifications of the small vessel walls and those concerning the physical qualities of the contents (sludge phenomenon or disturbance of the mobility hematose) can explain the decrease of permeability.

Under a fine analysis we found a relative lowering of the capillary resistance in people with hypertension and elderly diabetics, something other authors have found in adults. Whatever the results we should take into account the therapeutic activity of Endotelon and its effects on an aging population.

In this clinical study of this product we conserved the angiosterrometric apparatus of Parrot as an appreciable and essential element, reserving for a few patients (18 out of 46) a compliment of the investigation for the Landis test on the variations of capillary permeability. It appears very strongly and very clearly that Endotelon had a favorable action on the subjects who clinically displayed the problems of capillary fragility and/or a lowering of capillary resistance on the angiosterrometer.

The Endotelon activity seemed to be more reliable as the age was less elevated. The percentage of good results increased as a function of time to attain, it would seem, a maximum efficiency between 30 and 45 days of treatment with certain patients making it necessary to take 150mg a day. This happened even though the majority of the positive results were obtained with a dosage of 100mg a day with some even being as low as 30mg. Finally we put into evidence a residual activity of the product since 21 out of 31 very good results were maintained 15 days after stopping the treatment.

Tolerance was excellent in all the cases save one on the clinical plan and excellent on the biological plan.

It is interesting to note a confirmation of the therapeutic activity of Endotelon carried out using a double blind test.

#### IV CONCLUSION

In light of our current knowledge of microcirculation and of certain substances like vitamin P, especially flavanoids, we believe that we have shown the benefits of using Endotelon during capillary fragility problems thanks in particular to the Parrot angiosterrometer. We have also added using the Landis test the proof of the efficiency of this product against capillary permeability.

It appears that apart from Endotelons excellent clinical and biological this product is capable of normalizing capillary permeability and fragility problems through a dose of 100mg a day. The latter can be detected without clinical signs by the use of an angiosterrometer. The average length of treatment should be 30 days. The residual action of the product permits discontinuing use 20 days a month.

Our study was carried out on a geriatric population that showed evidence of and increase in capillary resistance and an improvement of capillary permeability. The elderly subject did not display any pathological alteration of the microcirculation. We found in each case in this study that the results of Endotelon were easier to acquire the younger the subject was.

This study allowed us to show that taken daily Endotelon deserves to be used in all cases of clinical manifestations of peripheral microangiopathy (broken blood vessels, Bateman purpura, recurring ecchymosis), all problems of capillary permeability when the capillary fragility is manifested through the measurements of an angiosterrometer.

Endotelon, OPC grape extract, appears to us to be the best microangioprotection in the elderly and has a perfect biological and clinical tolerance, so precious in geriatric care.

Please note: In France Endotelon is made from OPC extracted from Grape Seeds