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The CO_2 Level as a Factor Stimulating Angiogenesis. Phenomena of Tissue Regeneration and Destruction.

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Abstract

The regeneration of vessels and their development occur in places of their destruction. This phenomenon suggests that the destruction process itself stimulates vascular development and entails tissue healing and self-repair. Understanding the phenomena of self-repair is extremely important in the process of restoring tissues and organs to the proper functioning of individual organs and the entire body. Therefore, the recognition of angiogenesis processes seems to be the key in the treatment of many diseases.

Many years of research on blood vessels, their development and mineralization (Pawlikowski 1987, 1993, 1999, 2003, 2018, 2019, 2020a, 2020b, Pawlikowski, Ryskala 1991, Pawlikowski, Pfitzner 1999, Pawlikowski et al. 1995 a, b, c), bone mineralization, demineralization and the process of bone healing (Niedźwiedzki, Pawlikowski 1990, Niedźwiedzki et al. 1993, Pawlikowski, Niedźwiedzki 2002), as well as the phenomena of tumor mineralization (Pawlikowski, Niedźwiedzki 2002, Pawlikowski 1991d, 2011, 2013, 2019, 2020b), have all provided a lot of observations on angiogenesis. The presented publication is a summary of many years of early research.

Views on the role of endothelium in angiogenesis are widely published (Gerhardt et al. 2003, Bajaj et al. 2014, Labov et al. 2018, Bai et al. 2020). Various substances have been proposed as a factor in the development of arteries, including vitamin D3. An important role in the development of angiogenesis is also attributed to perisytes, i.e. unorganized stem cells present in the vicinity of blood vessels (Bergers, Song 2005). The literature in many publications also reports on the formation of new vessels in neoplastic tissues (Pawlikowski, Niedźwiedzki 2002, Thurston, Kitajewski 2008, Servan-Schreiber 2012, Pliquigi et al. 2020, Unterleuthner et al. 2020). The literature also provides examples of phenomena that inhibit the development of angiogenesis (Benedito et al. 2009), often based on their computer modeling (Motherwell, Murfee 2018, Carpentier et al. 2020).

Literature information and the results of own research suggest a similar cause of angiogenesis in various cases of vascular formation. This view will be presented below.

Vascular Development in the Areas of their Blockage

Collateral Circulation

In vessels blocked by substances crystallizing in them (Pawlikowski, Pfitzner 1999, Pawlikowski 2020a), e.g. coronary vessels, the level of CO_2 increases. This is the result of hypoxia, i.e. a change in the ratio between the oxygen level and the CO_2 level at the point of blockage. Therefore, in the area of the artery blockage the oxygen level is low compared to the CO_2 level, which increases as a result of the death of myocardial cells. Consequently, this phenomenon leads to the formation of easily dissociating carbonic acid (H_2CO_3), formed from the local CO_2 and water present in the tissues. As a result of this, the pH of the environment drops below 7.0. The angiogenesis itself, developing at the site of arterial blockage, can lead to the formation of collateral circulation (Photo 1).

In the case of neoplastic tumors, the newly formed concentrations of cells form numerous blood vessels

that develop from both primary and secondary vessels (Photo 2). The rate at which these blood vessels form is often slower than the rate at which new cells are formed. That results in an increase in non-discharged CO_2 causing local acidification of the environment.

The phenomena described in this publication and their interpretation are based on studies of damaged arterial walls. It was noted that a damaged (for various reasons) artery wall may heal itself. The endothelial surface, which proliferates as a result of angiogenesis, forms particular structures that in further evolution lead to the formation of a new artery (Photo 3).

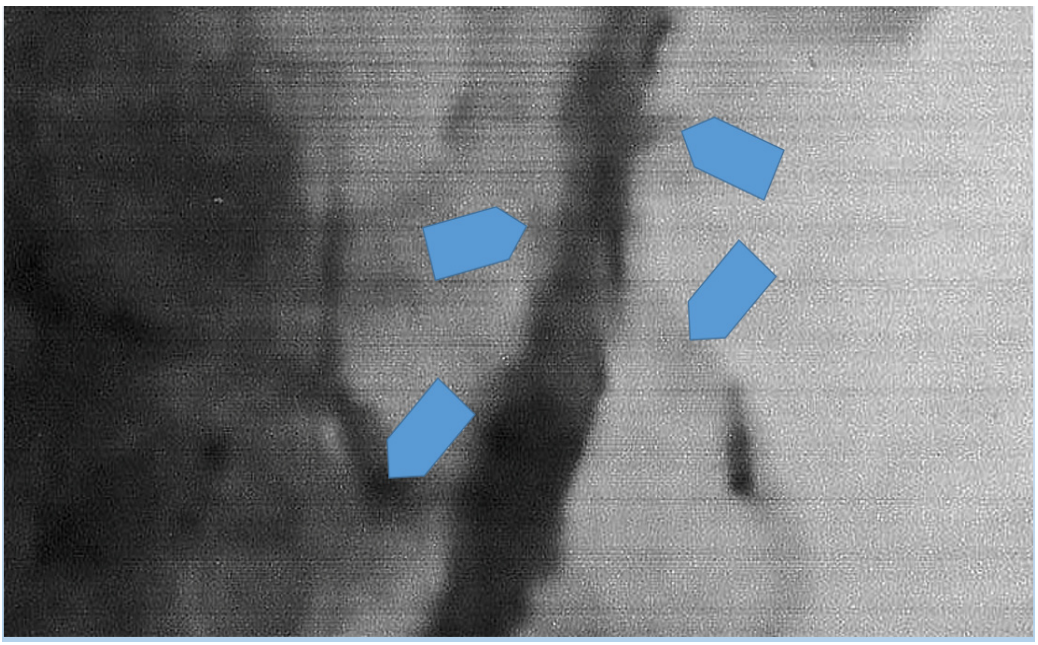

Photo1. *Development of secondary vessels (arrows) near a blocked coronary artery. Magnification 150x.*

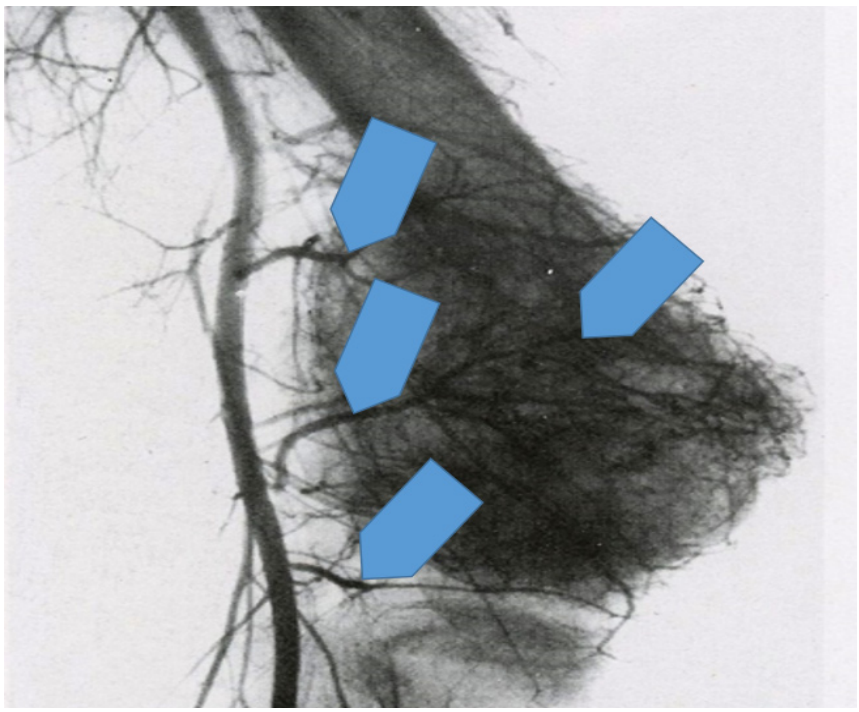

Photo2. *Numerous secondary blood vessels in the Liczne, wtórne naczynia krwionośne in a tumor of the lower base of thigh (Pawlikowski, Niedźwiedzki 2002).*

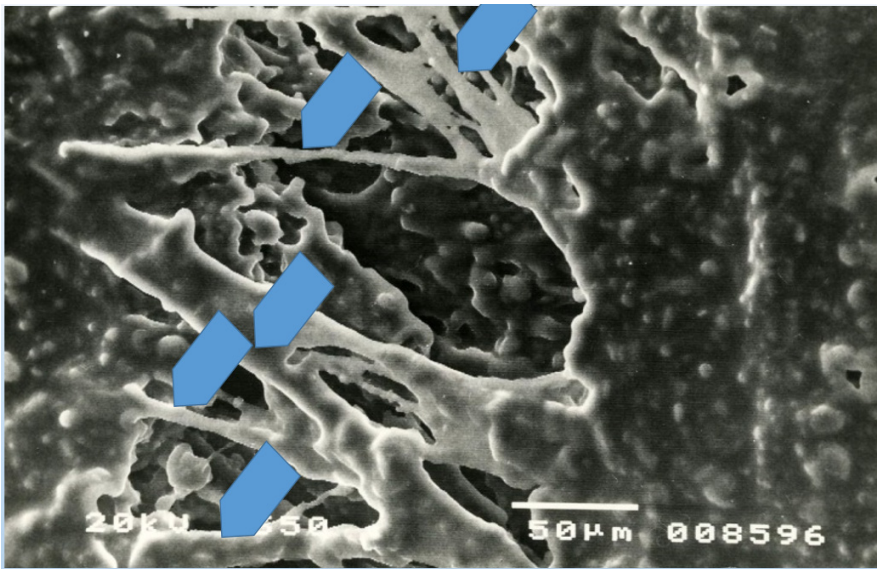

Photo3. *Endothelial growth phase at the site of damaged artery wall. Arrows show endothelial proliferation of the damaged artery. Scanning microscope, magnification according to scale.*

The Phenomenon in the Cell Membrane of Intima

Endothelium is the site of many biochemical phenomena. One of the most important is the synthesis of prostacyclins, prostaglandins and thromboxanes, which are secreted into the blood and regulate its properties, including coagulability and the ability to aggregate. Research shows that individual elements of the cell membrane of intima have different functions (Fig. 1).

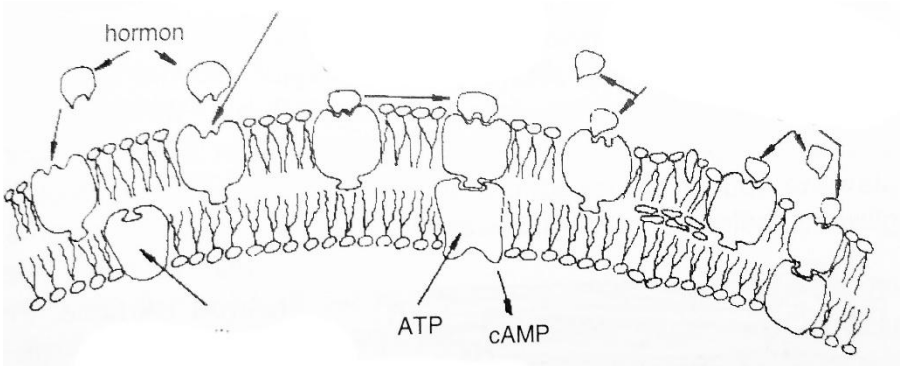

Fig1. *A general structure of a fragment of the intima cell membrane (after: Wetulani 1983)*

Angiogenesis in a Blocked Artery (E.g. Coronary Vessel)

Concentrations of cholesterol crystallizing in and on the artery wall can inhibit blood flow. This causes local increase in CO_2 content in relation to the content of oxygen, which is not supplied by the blocked artery. The phenomenon causes local CO_2 to react with water, leading to the formation of carbonic acid (H_2CO_3). It dissociates easily and breaks down into free protons (H^+) and CO_3^{2-} carbonate groups. The above phenomena lead to a decrease in the local pH and development of acidic environment that is aggressive towards the artery, where the flowing blood has a pH of 7.2-7.3. The result is that the acidic environment damages the endothelium of the artery.

The place of damage (destruction) of the artery endothelium is the site where interatomic bonds of its biological structures are broken. Due to broken bonds in the area of destruction an electric field appears, i.e. a place where free protons, carbonate groups etc. can be attached. Thus, the site of endothelial damage is the center in which the construction of new endothelium and consequently new vessel takes place (Fig. 2).

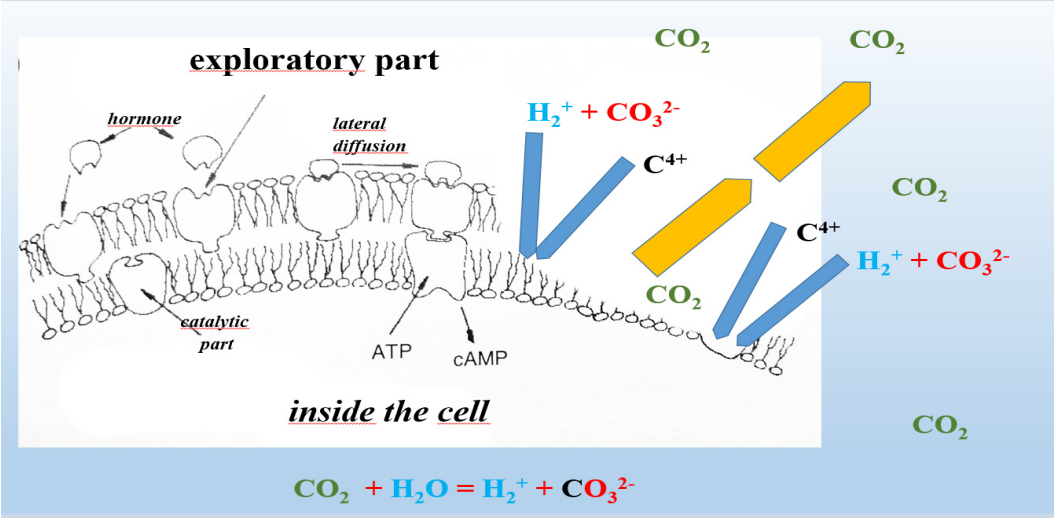

Fig2. *Generation of angiogenesis (collateral circulation) at the site of damage to the blocked artery (description in the text).*

Protons and carbon from the CO_3^{2-} groups build new biological structures at the site of damage to the endothelial cell membrane (blue arrows). The newly formed vessel (artery) proliferates in the direction shown by the yellow arrows.

Angiogenesis in Cancerous Tumors

In the case of angiogenesis in cancerous tumors, the phenomenon is similar. However, the cause of the local increase in the level of CO_2 is different than in the case of artery blockage. Here, the reason is the huge number of cells that multiply, each of them producing carbon dioxide in its life processes. The locally existing blood vessels are not able to evacuate the excess, which results in an increase in its quantity. The next stages of the phenomenon of angiogenesis generation and development proceed as described above, in the case of arterial blockage (Fig. 3).

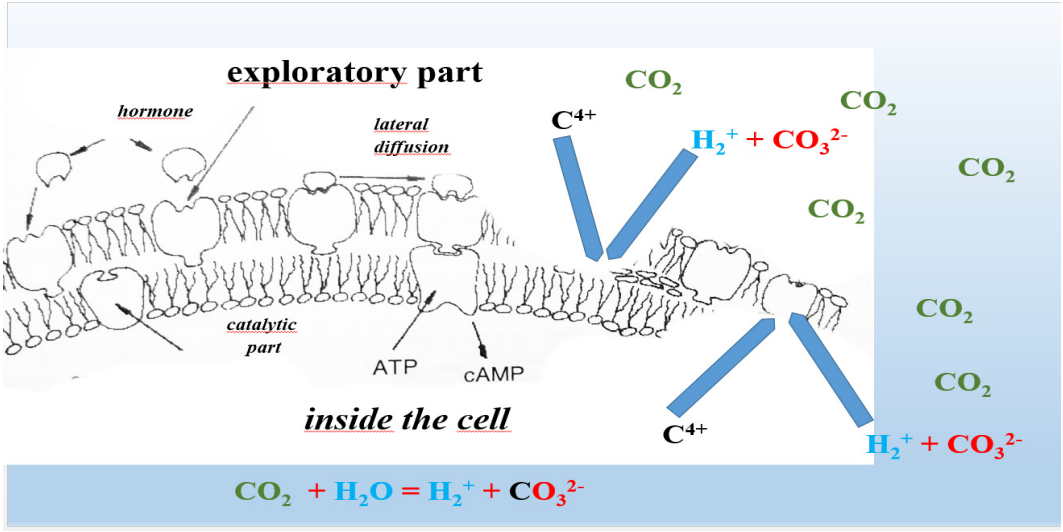

Fig3. *Development of angiogenesis in an oncological tumor (description in the text).*

Damaged endothelium proliferates using "local material" in the form of protons and carbon to rebuild and initiate a new vessel.

Angiogenesis in a Broken Bone

While the cause of angiogenesis in bone fracture healing is different, it actually comes down to the phenomena described above for blocked arteries and tumors. In this case, there is also a local increase in the CO_2 level. It is caused by the rupture of blood vessels during the fracture. The environment at the fracture site (especially in the fracture gap) contains an increased

amount of CO_2. This is caused by the inability to drain it through damaged vessels. Increased amount of carbon dioxide leads to the formation of dissociating carbonic acid and the phenomenon continues as described for blocked arteries and tumors.

Due to the fracture, the arteries are damaged mainly in the form of ruptures. Thus, the damage occurs at the tips of the broken arteries, and that is where angiogenesis begins. As a result, the proliferation of newly formed vessels in the fracture zone takes place from the bone fracture to the bone fracture (Fig. 4). The process of angiogenesis itself is similar to that in tumors and blocked vessels.

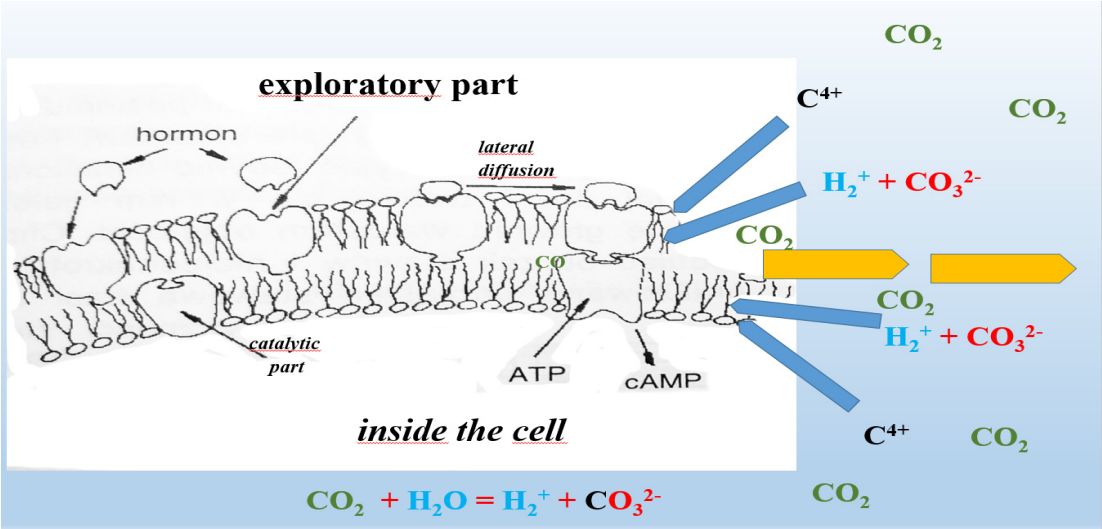

Fig4. *Generation of angiogenesis in bone fracture (explanation in the text).*

The phenomenon of new artery generation in the artery endothelium at the site of vessel rupture. Material for the newly developing artery is collected from the local environment (blue arrows). The direction of growth of the newly formed vessel runs roughly from one bone fragment to the other (yellow arrows).

Conclusions

1. Angiogenesis develops in areas with arterial damage, i.e. places where excess CO_2 cannot be discharged through damaged vessels (veins). Another area with excess CO_2 are cancer tissues, where the levels of CO_2 raise due to fast increase in number (proliferation) of cells.
2. Locally high level of CO_2 leads to the formation of aggressive carbonic acid H_2CO_3, which can destroy the cell membrane of endothelial cells.
3. Damaged areas are places where the atomic structures of the organic components that make up the intima cell membrane have a broken interatomic bond.
4. These damaged areas in the structure of endothelial cell membranes are endowed with electric charges. This is where the formation of new vessels (angiogenesis) starts.
5. The "building blocks" for the development of new vessels are hydrogen and calcium from easily-dissociated H_2CO_3 that is created from the excess CO_2.
6. Depending on the cause of the arterial damage, angiogenesis develops along the axis of the vessel (in fractures) or in multiple directions (collateral circulation of blocked arteries or neoplastic tissue).
7. Considering the above observations, it is possible to accelerate or inhibit the development of angiogenesis by regulating the local level of CO_2.
8. If it is necessary to accelerate angiogenesis, the CO_2 level in the area of the blocked artery or bone fracture should be locally increased.
9. If it is necessary to stop angiogenesis, the locally produced carbonic acid needs to be neutralized. This is important in blocking tumor angiogenesis and thus fighting the disease.
10. Separate studies are required to fully identify methods of accelerating and blocking angiogenesis.

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