



How could a Basic Knowledge of Vascular Physiology Provide a New Tool for Tumor Oxygen-induced Radiosensitization- Postocclusive Reactive Hyperemia Concept for Synchronized Radiotherapy

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How could a Basic Knowledge of Vascular Physiology Provide a New Tool for Tumor Oxygen-induced Radiosensitization- Postocclusive Reactive Hyperemia Concept for Synchronized Radiotherapy

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Abstract

Tumor angiogenesis leads to the development of pathologic vessels and blood flow insufficiency that results in tumor hypoxia, which can be an obstacle for effective radiotherapy. Tumor perfusion enhancement, through increased oxygenation, is a recognized method for tumor radiosensitization, but no clinically efficient means to achieve this have been reported to date.

Since tumor-feeding arterial vessels are normal host vessels, postocclusive reactive hyperemia, a well-known physiologic phenomenon in which blood flow rises secondary to the release of arterial occlusion, could be used judiciously in order to temporarily increase the perfusion and oxygenation of a tumor situated downstream of an arterial occlusion site. Perivascular or endovascular vascular occlusion can easily be adapted to each tumor location or size, for easy synchronization of ionizing radiation to the tumor oxygenation peak, either acutely or chronically (i.e., repeated episodes of occlusion, reperfusion and reoxygenation).

Thus, postocclusive reactive hyperemia could be an ideal method for tumor perfusion enhancement, as it may combine the desirable characteristics of selectivity, reversibility, and predictability and it can be applied widely throughout the body.

Hypothesis

Introduction

Tumor hypoxia (1-5) is an obstacle to the efficacy of oncology therapies -principally radiotherapy (6-9)-and has been the subject of extensive research since the essential effect of oxygen on the effect of ionizing radiation was first discovered (10) more than 50 years ago. The concurrent presence of oxygen with irradiation augments the radiation-induced damage of deoxyribonucleic acids (DNA) within tumor cells and

can increase radiotherapeutic efficacy up to 3-fold compared with irradiation of hypoxic tumor cells (1,10,11). Hence, the therapeutic enhancement of tumor oxygenation during radiation sessions is one of the major challenges of the radiotherapy field.

Tumor hypoxia is important due to the reduction in oxygen supply to the tumor (12, 13), induced by highly abnormal, chaotic and heterogeneous intratumoral vasculature (14-18), with vessels that are very often dilated, tortuous, abnormally branched, with high endothelial permeability, blind-ends, arteriovenous shunts or intussusceptions (18). All of these vascular architectural abnormalities contribute to acute cyclic episodes of hypoxia (18-21) (or perfusion mediated hypoxia), with classically intermittent, or even non-perfused tumor vessels (22). In addition to abnormalities of the vessel structure, vessel compression -by adjacent growing tumor cells (23), and/or elevated interstitial pressure (24), secondary to the absence of lymphatic vessels in the tumor, hyperpermeability of tumor vessels (25-27)- and vessel vasomotion (18-20)(i.e., spontaneous vasoconstriction of tumor arterioles) contribute to arterial blood flow insufficiency throughout the tumor.

Increased perfusion into tumor feeding artery(ies) is thus naturally one of the possible ways to raise global oxygen partial pressure in the tumor (13, 28-32). Previous investigations have focused mainly on pharmacological enhancement of tumor blood flow, based essentially on the actions of vasoactive drugs on the vasculature of the tumor and/or neighbouring tissues, but these have not proven effective. Indeed, intratumoral blood flow exhibits highly unpredictable responses (28-33). For example, the use of vasoconstrictors drugs can either increase tumor perfusion (33, 34)-by redistribution of neighbouring vascular bed blood flow through the tumor, secondary to the vasoconstriction of the former vascular bed, if tumor vessels do not react to drugs-, or even decrease it (33, 35)-due to intratumoral vasoconstriction, if the tumor vessels express the appropriate drug receptors and can react to the drug. Similarly, vasodilators can

either increase (36, 37), or decrease tumor perfusion (38, 39), independent of the effect on intratumoral blood vessels, secondary either to reduction of arterial blood pressure (38) –thus reducing the perfusion of tumor feeding arterial vessels-, or by vascular steal (39), referring to steal of tumor blood flow through normal neighbouring vascular bed, in which the vascular resistance decreases more than tumor vessels. Moreover, the complex interaction between the tumor and the neighbouring vascular bed (situated in parallel and/or in series) (33), structural abnormalities of the tumor vessels -such as, a paucity of vascular smooth cells or very loose coverage of endothelial cells by pericytes (25, 40-42)-, make it hazardous or difficult to utilize such a strategy based on the modification of tumor vascular tone via pharmacological means (33, 39), which is consequently unselective for most of them, and makes the timing and intensity barely controllable.

The ideal method of tumor perfusion enhancement (31) should exhibit selective actions, be reversible, controllable and have predictable effects, and should be useful for most solid tumors. Herein, I describe a new hypothesis that could fulfil those criterias, based on the use of postocclusive reactive hyperemia (PORH), a well-known physiologic vascular phenomenon.

Postocclusive Reactive Hyperemia -

Concept for Synchronized Radiotherapy

A/ Description (Fig.1.2.3.4.5.6.)

The occlusion of an artery upstream of the tumor or tumor organ (Fig.1.2.), will induce vasodilatation of the distal vascular bed, including the tumor feeding artery(ies) (which are normal host vessels), decreasing its vascular resistance, thus reactive hyperemia will occur after release of the occlusion (Fig.3.) through the whole downstream vascular bed, and enhance intratumoral blood flow. At the moment of peak tumor hyperaemia, which will occur rapidly after release of the occlusion, tumor oxygenation will be maximal, and the tumor should be targeted by synchronized ionizing radiation, which will thus increase the efficacy. Tumor perfusion and oxygenation will subsequently progressively return to normal (Fig.4.).

Repetition of vascular occlusions will be possible due to chronic placement of a perivascular occluder (Fig.5.) or an endovascular balloon catheter (Fig.6.), connected to a subcutaneous port. Transcutaneous puncture of the port will permit easy control of tumor vascular flow for ideal synchronization with the irradiation, and the occlusion technique will be selected principally related to the diameter of the artery targeted for occlusion (preferentially,

endovascular occlusion for small arteries or arteries that are not accessible through surgery, and perivascular occlusion for larger arteries or arteries that are more easily accessible).

B/ Mechanism of Tumor perfusion enhancement by PORH

Tumor angiogenesis is absolutely necessary for tumor growth (43, 44), particularly for those above 1 mm diameter in size. Tumor-feeding vessels are co-opted host vessels, which are also incorporated into the tumor (31, 33, 45-47). As those host vessels exhibit normal architecture and functionality, postocclusive reactive hyperemia is at least theoretically possible in these vessels.

PORH is a ubiquitous phenomenon, demonstrated for the first time in 1872, by Julius Friedrich Cohnheim, as skin flushing following arterial occlusion (48). Numerous organs, e.g. limbs (49), heart (50), brain (51), liver (52), or kidney (53) also exhibit reactive hyperemia. It is already used in cardiovascular field to trigger and test flow-mediated vasodilatation as a tool for the assessment of arterial endothelial function (54), and has more recently been used by critical care physicians to test microvascular reactivity during sepsis (55). It is simply realized regularly by brachial artery cuff occlusion for 3 or 5 minutes to induce distal ischemia and concomitant vascular bed tone reduction. After release of the cuff, the previously relaxed downstream vascular bed undergoes an acute and temporary hyperemia as the flow rises above the preocclusion level. The mechanism(s) involved in PORH are complex, the two principal supposed mechanisms (49) are a myogenic vasodilator response (the Bayliss effect) (56, 57) (arterioles and small arteries dilate in response to a decrease in transmural pressure in order to equilibrate the vessel wall tension), and ischemia-induced synthesis of vasodilator metabolites (58, 59). PORH is followed rapidly by flow-mediated dilatation (60) of the hyperaemic vascular bed that lasts for several minutes until flow progressively returns to a basal level; in parallel, the distal bed vascular resistance returns to its initial level due to an inverse myogenic response (vessel constriction), and dilution of the ischemia-induced vasodilator metabolites.

Hence, PORH can certainly occur upstream and provide blood flow into a tumor, thanks to arterial vessels that may react by vasodilatation during the vascular occlusion, and accept the increased flow due to their decreased resistance:

Hypoxic vasodilatation (61) has been demonstrated in peritumoral feeding arteries in rat brain tumors, inducing increase perfusion (blood volume) in the tumor periphery, these arteries are comprised of

vascular smooth cells that are normally reactive. Similar to the hypoxic stimulus, the vascular occlusion (i.e., stagnant hypoxia) used in PORH also induces a strong intravascular desaturation of haemoglobin (55); moreover, a supplementary myogenic vasodilatation response is the rule in the case of PORH, in addition to the ischemic stimulus (49, 58). Indeed, the increase in blood flow is generally less than 2-fold for forearm blood flow during hypoxia-induced vasodilatation (62, 63), whereas it is generally 6-fold for peak brachial arterial flow during PORH (64), and up to 17-fold with further distal ischemic stimulation (65). The degrees of downstream vasodilatation and increase in blood flow are directly proportional to the degree and duration of the ischemic stimulus (65). Thus, PORH has physiological reasons for further inducing increased flow in the tumor, in response to the level and duration utilized (65).

Second, a supplementary argument to support the potential of PORH in the tumor vasculature comes from microvascular reactivity studies of septic patients. In some aspects, microvascularization of septic shock patients mimics tumor vascularisation (66): during sepsis, microvascular blood flow becomes heterogeneous, with intermittently circulating and non-perfused capillaries; oxygen supply is thus impaired, as in tumor, secondary to microvascular blood flow-deficiency. Microvascular reactivity of these patients appeared to be blunted, but not abolished (55, 67); suggesting that PORH can occur, even with a pathologically-impaired microcirculation.

In contrast to pharmacologic modulation of tumor blood flow, PORH has the potential to fulfil several important criteria of the ideal method of tumor perfusion enhancement:

-Selectivity (the nearer the tumor feeding artery(ies) is/are to the occlusion site, the more local the blood flow and oxygenation enhancement, excluding the neighbouring vascular bed)

-Spontaneous reversibility

-Predictability and Modulability (since PORH intensity can be increased or decreased by increasing or decreasing the downstream ischemic vascular bed length, between the occlusion site and the tumor vascular bed, respectively; in the same manner, the duration of hyperemia can be increased by increasing the duration of ischemia, and vice-versa)

-Utility for all tumoral locations and sizes (due to the technical potential of endovascular or perivascular occlusion)

Thus, PORH-induced enhancement of tumor perfusion could be particularly well-adapted to radiotherapy sessions, as synchronization become reality.

C/ Problems brought about by the concept

1. Vascular steal (Fig.7.)
2. Radiation-induced injury of normal tissues
3. Ischemia-reperfusion injury of the tumor
4. Reactivity of intratumoral vessels to temporary vascular occlusion

This hypothesis of PORH through the tumor brings about several interesting questions that will need specific experiments, and may limit the success of the concept:

-First, vascular steal (Fig.7.) could occur during PORH. Neighbouring vascular bed blood flow may increase secondary to PORH, and either prevent the increase in tumor flow, or induce a reduction in tumor perfusion, as in experiments using vasodilators drugs (38, 39) for modification of tumor vascular tone. As the degree of PORH becomes less selective, the decrease in neighbouring vascular bed resistance will become more extensive, and the possibility of vascular steal will increase –especially if the basal tumor vascular resistance remains high (24-27), despite the diminution of tumor feeding arterial resistance -; conversely, the solution -that could consist of decreasing the distance between arterial occlusion site and the tumor feeding artery(ies), to avoid affecting reactivity of the neighbouring vascular bed - may reduce the tumor perfusion enhancement effect since vasodilatation will occur within a shorter ischemic segment of the vascularised tissue (including the tumor), and may thus be diminished (analogous to the physiology of normal tissues (65, 68)).

-Second, the increase in oxygenation of neighbouring tissues, downstream of the occlusion site –if PORH is not completely selective- could increase undesirable radiotherapy injury in normal tissues. However, in reference to the relationship between tissue oxygen partial pressure and radiosensitivity (1, 10), further increase of oxygenation in previously well-oxygenated tissues induces a non-significant increase of radiotherapy-induced damage. Nevertheless, PORH should be used carefully, and consist of vascular occlusion as near as possible to the tumor, avoiding the eventually counterproductive strategy of vascular steal and radiotherapy injury of normal tissues.

-Third, PORH -even after a short period of vascular occlusion- will induce ischemia-reperfusion injury (IRI) throughout the tumor. Although the antitumor effects of IRI via intratumoral production of reactive oxygen species have been demonstrated (69, 70), enhancement effects of IRI on tumor growth can also occur (71). Furthermore, IRI appears to alter tumor microvascularization and tumor blood flow recovery after a prolonged ischemia (69). However, the expected duration of ischemia in PORH to elicit the consequent perfusion increase, is much faster (less

than 3 minutes), compared to the classical duration of IR in animal or clinical experiments (at least 30 min), and thus the impact of IRI on tumor (both negative and positive effects) should be much less significant.

-Fourth, will intratumoral vessels (which are pathological vessels) react (by constriction or dilatation) to temporary vascular occlusion and reactive hyperemia of upstream vessels? Is the vasculature of the tumor active or passive during vascular occlusion? These two hypotheses are that the tumor vasculature may oppose -by constriction- or permit -by dilatation- the tumor perfusion enhancement. The increased flow to the tumor may be proportional to the number of host vessels relative to the tumor vessels -as has been hypothesized in vasoactive drug experiments for tumor flow enhancement (29-39)-, since host co-opted vessels may react physiologically, whereas the angiogenic vessels may not.

Conclusions

PORH has never been enounced nor explored as a possible strategy for enhancement of tumor perfusion and overcoming tumor resistance to radiotherapy; however, it may be a powerful, easy, and reproducible tool thanks to the ubiquitous characteristic of this physiologic phenomenon of the vasculature

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Illustrations

Illustration 1

Figure 1

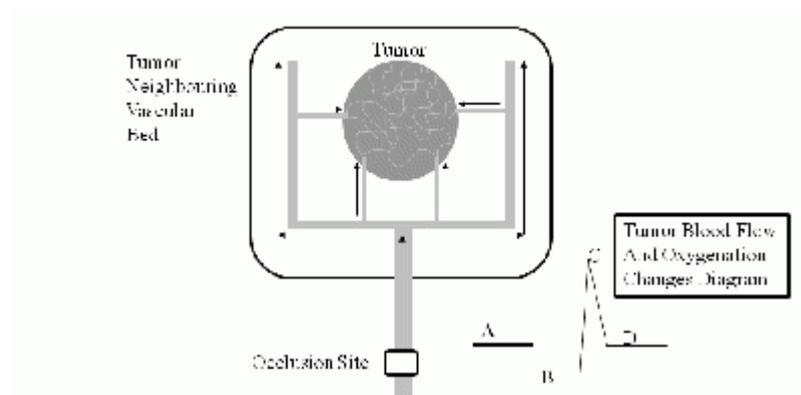


Fig.1. Simplification of the Tumor and neighboring vascular bed flow (Basal state A). The diagram represents the relative changes of tumor blood flow and oxygenation into tumor feeding arteries, as a function of time. (PKR), steps: A. Basal value, B. Vascular occlusion-induced no flow, C. (Peak) Hyperemia after release of the occlusion, D. Return to the basal level. Gray line indicates the vessels; darkness is proportional to the flow value. Black arrows: vascular flow (thickness is proportional to the flow). Tumor darkness is proportional to its blood flow and oxygenation. Occlusion Site is somewhat upstream of the tumor.

Illustration 2

Figure 2

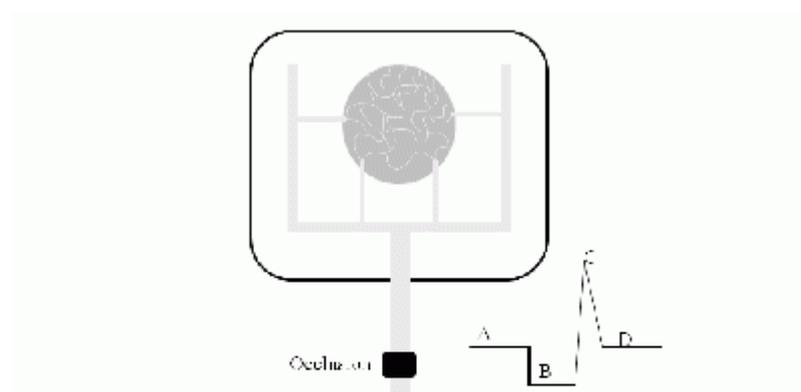


Fig.2. Intratumoral no-flow induced by upstream temporary vascular occlusion. Tumor becomes temporarily globally anoxic, while occlusion decreases resistance of the downstream vascular bed, secondary to the myogenic response and ischemia-induced production of metabolites along the vascular bed.

Illustration 3

Figure 3

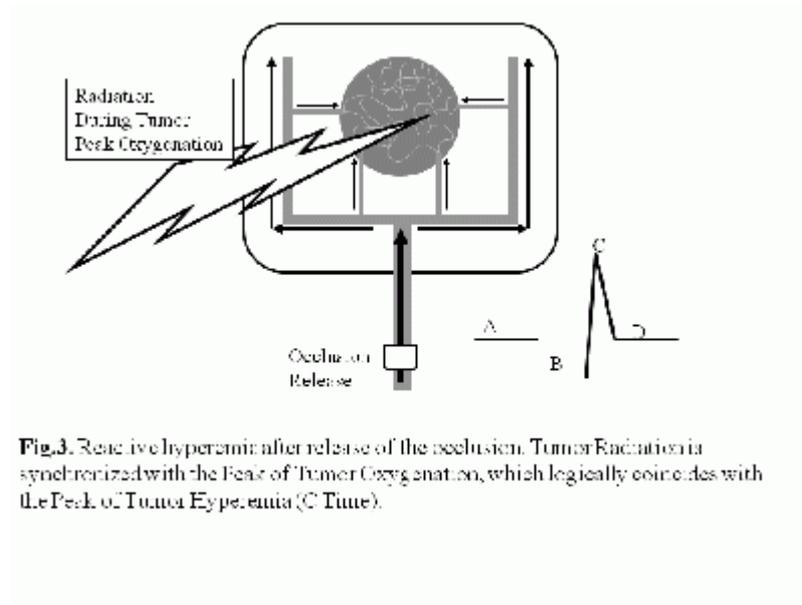


Fig.3. Relative hyperemia after release of the occlusion. Tumor Radiation is synchronized with the Peak of Tumor Oxygenation, which logically coincides with the Peak of Tumor Hyperemia (C Time).

Illustration 4

Figure 4

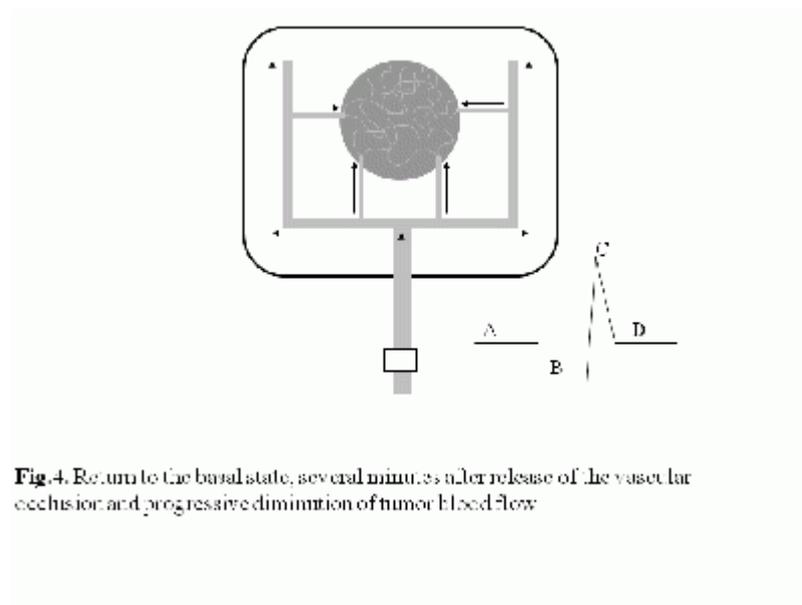


Fig.4. Return to the basal state, several minutes after release of the vascular occlusion and progressive diminution of tumor blood flow.

Illustration 5

Figure 5

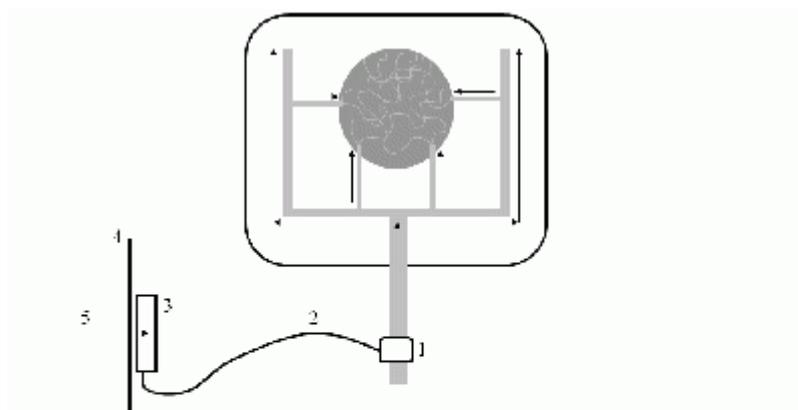


Fig.5. Installation of the perivascular occluder around an artery upstream of the tumor by surgery (deflated state). The artery is occluded by completely inflating the silicone balloon of the occluder with saline, and the occlusion is then released by deflation. 1. Perivascular occluder, 2. Occluder tube, 3. Subcutaneous port, 4. Skin, 5. Transcutaneous puncture of the port for occluder inflation/deflation. Use of the perivascular occlusion can be applied repeatedly as necessary.

Illustration 6

Figure 6

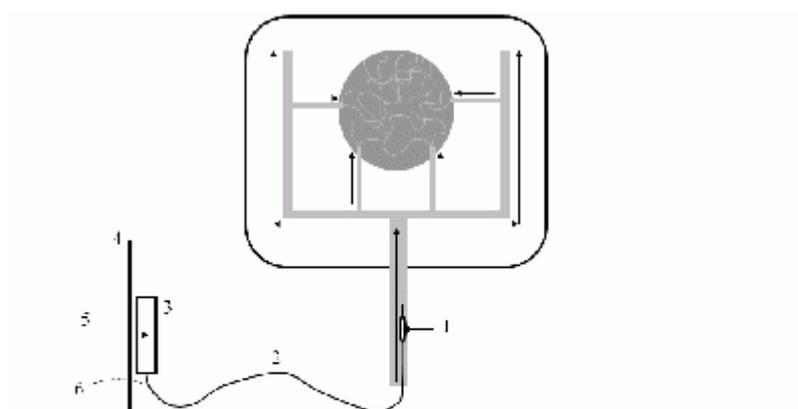


Fig.6. Endovascular balloon catheter installed in an artery upstream of the tumor (deflated state). The artery is occluded by completely inflating the balloon with saline, and the occlusion is then released by deflating it. 1. Endovascular balloon, 2. Catheter, 3. Subcutaneous port connected to the catheter, 4. Skin, 5. Transcutaneous puncture of the port for balloon inflation/deflation, 6. Percutaneous route to the temporary catheter during acute use. An endovascular catheter should be inserted preferentially in the artery mode (6.) to avoid arterial thrombosis.

Illustration 7

Figure 7

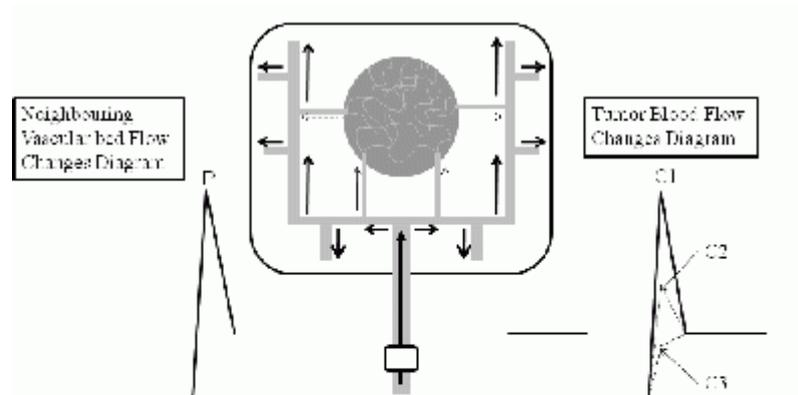


Fig.7. Vascular Steal in non-selective PDRH, secondary to the decrease in resistance of the vascular bed neighbouring the tumor and parallelism between the tumor and neighbouring vascular beds. The expected peak tumor hyperemia induced following release of the vascular occlusion (C1) could in reality be blunted (C2) compared to the peak neighbouring hyperemia (P line) and C1. Furthermore, in case of the reversal of flow into some tumor feeding arteries (black dotted arrows), tumor blood flow could be further reduced temporarily (C3) below the normal level.

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