Review

Myocardial blood flow in patients with hibernating myocardium

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Abstract

The debate on whether resting myocardial blood flow (MBF) to hibernating myocardium is reduced or not has attracted a lot of interest and has contributed to stimulate new research on heart failure in patients with coronary artery disease (CAD). Positron emission tomography with oxygen-15 labeled water ($^{15}$H$_2$O) or nitrogen-13 labeled ammonia ($^{13}$NH$_3$) has been used for the absolute quantification of regional MBF in human hibernating myocardium. When hibernating myocardium is properly identified, i.e. a dysfunctional segment subtended by a stenotic coronary artery that improves function upon reperfusion, the following conclusions can be reached based on the available literature: (a) in the majority of these studies resting MBF in hibernating myocardium is not different from either flow in remote tissue in the same patient or MBF in normal healthy volunteers; (b) a reduction in MBF of $\sim$20% compared to MBF in remote myocardium or age matched normal subjects has been demonstrated in a minority of truly hibernating segments; (c) hibernating myocardium is characterized by a severely impaired coronary flow reserve which improves after revascularization in parallel with contractile function. Thus, the pathophysiology of hibernation in humans is more complex than initially postulated. The recent evidence that repetitive ischemia in patients with coronary artery disease can be cumulative and lead to more severe and prolonged stunning, lends further support to the hypothesis that, at least initially, stunning and hibernation are two facets of the same coin.

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1. Introduction

The debate on whether resting myocardial blood flow (MBF) to hibernating myocardium is reduced or not has attracted a lot of interest and, undoubtedly, has contributed significantly to stimulate new research on heart failure in patients with coronary artery disease (CAD). Although the debate is not over yet, some of the initial paradigms have been proven incorrect while new pathophysiological concepts have emerged.

2. The initial hypothesis

There are a number of techniques available for measuring coronary blood flow in man [1], most of which involve cardiac catheterization procedures. These measurements are usually performed using Doppler catheter [2,3], quantitative coronary arteriography [4] and thermodilution [5]. Although multiple regional measurements can theoretically be made in the different coronary arteries in real time using Doppler catheter and quantitative coronary arteriography, these methods measure epicardial coronary flow velocity or coronary blood flow as opposed to tissue perfusion as the mass of myocardium supplied by the artery under study cannot be defined. The same limitations apply to coronary sinus thermodilution.

A number of radionuclide imaging techniques have emerged for the assessment of regional MBF [6]. Their non-invasive nature and the ability to provide simultaneous information on the three different coronary beds have contributed to their widespread application in patients with coronary artery disease. The initial hypothesis that hiberna-
ion is due to a down-regulation of myocardial function secondary to a reduction of resting MBF [7] was supported by a series of studies in which semiquantitative measurements of MBF were performed using different radioactive flow tracers with single photon emission tomography (SPET) (see Ref. [8]). Although radionuclide imaging techniques like thallium-201 SPET enable the assessment of nutritive tissue perfusion, they can only provide images that reflect relative regional radioactivity concentration rather than enabling measurement of absolute MBF (i.e. ml/min/g) [9]. The definition of abnormal regional uptake is based on the demonstration of a contrast between two ventricular segments and not an absolute reduction in uptake compared to normal reference values. Therefore, an apparent reduction of radioactivity concentration in one region may reflect higher uptake in the reference region rather than an absolute reduction in the ‘defect’ itself. In addition, the fact that chronically dysfunctional segments are generally thinner than remote normally contracting myocardium will contribute to increase artificially the difference between hibernating and remote myocardium as a consequence of the partial volume effect [10]. This occurs whenever the dimension of the object to be imaged (in our case the thickness of the left ventricular wall) is comparable or smaller than the camera’s spatial resolution. Although the detector will accurately record the total activity in the object, it will distribute it over an area larger than the actual size of the object. Hence, the detected radioactivity concentration per unit volume will be less than the actual value [11].

3. Positron emission tomography (PET) and absolute myocardial blood flow

PET overcomes the physical limitations of previously available imaging systems by providing the means for accurate attenuation correction, thus enabling accurate quantification of the concentration of radiolabeled tracer in the organ of interest [12]. Photons traveling through a composite medium such as the thorax will be scattered by interaction with atomic electrons and undergo change of direction and loss of energy. If a photon is scattered it is ‘lost’ to the original line of response (the line joining the two PET detectors in coincidence) and the apparent radioactivity measured along that line of response will be less than the truth. This effect is known as attenuation. Scatter and attenuation are problems common to all radionuclide imaging techniques and are responsible for most of the artifacts associated with SPET, particularly when low energy isotopes (e.g. thallium-201) are used. In contrast to SPET, correction for attenuation is relatively straightforward in PET because of the mechanism of coincidence detection [11].

As PET technology has advanced and rapid dynamic imaging has become possible, quantification of MBF has been achieved following the development of suitable tracer kinetic models. Oxygen-15 labeled water (H\textsubscript{15}O) [13–16] and nitrogen-13 labeled ammonia (\textsuperscript{13}NH\textsubscript{3}) [17–20] are the tracers most widely used for the quantification of regional MBF with PET. Tracer kinetic models have been successfully validated in animals against the radiolabeled microsphere method for both H\textsubscript{15}O [13–16] and \textsuperscript{13}NH\textsubscript{3} [19,20]. Both H\textsubscript{15}O and \textsuperscript{13}NH\textsubscript{3} have short physical half lives (2 and 10 min, respectively) which allow repeated measurements of MBF in the same session [21].

4. MBF assessed with PET in healthy human subjects

The non-invasive nature of PET and the low radiation dose administered (5–10 times lower than that for SPET) allows the study of healthy human volunteers. The values of MBF determined using H\textsubscript{15}O and \textsuperscript{13}NH\textsubscript{3}, both at rest and during pharmacologically-induced coronary vasodilatation, are similar [22–25]. Similarly to previous studies in animals (Fig. 1) [26,27], PET has highlighted the heterogeneity of both resting and hyperemic MBF in normal human beings [28]. The latter issue has been recently investigated by our group in a large cohort (n = 160) of healthy volunteers of both sexes aged between 21 and 86 years [29] (Fig. 2). The results of this study can be summarized as follows: (i) In this population, baseline and hyperemic MBF are heterogeneous both within and between individuals; Baseline and hyperemic MBF exhibit a similar degree of spatial heterogeneity which appears to be temporally stable. (ii) Baseline, but not hyperemic, MBF is significantly higher in females than in males. (iii) There is a significant linear association between age and baseline MBF that is in part related to changes in external cardiac workload. (iv) Hyperemic MBF declines over 55 years of age. Notwithstanding the inter subjects variability, the short term repeatability of PET assessment of MBF within subjects has been well documented both under resting and hyperemic conditions [21,30]. These data, taken together, have important implications for the interpretation of myocardial perfusion studies in patients with hibernating myocardium.

5. Technical considerations on PET MBF measurements

5.1. The concept of flow per gram of perfusable tissue

In patients with previous myocardial infarction (a very common finding in patients with hibernating myocardium), the presence and amount of scar tissue within a dysfunctional region may affect the flow estimates made with PET particularly when liquid deposit tracers such as \textsuperscript{13}NH\textsubscript{3} are used whereas freely diffusible tracers such as H\textsubscript{15}O are less affected by this problem [16,31].
H$_{15}$O is a metabolically inert and freely diffusible tracer [31] that has a virtually complete myocardial extraction that is independent of both flow rate [32] and myocardial metabolism [15,33]. $^{13}$NH$_3$ is extracted from blood with an extraction fraction <100%, that is inversely related to the flow rate, and is then trapped in myocardial cells after conversion to $^{15}$N-labeled glutamine, a process mediated by adenosine triphosphate (ATP) and glutamine synthetase [19,33]. Thus, the extent of $^{13}$NH$_3$ metabolism depends on myocardial ATP stores. When H$_{15}$O is used, MBF is estimated from the tracer’s washout from the myocardium while in the case of $^{13}$NH$_3$, MBF is calculated from the tracer’s uptake by myocardium. These differences are of little relevance when the measurements of MBF are performed in normal myocardium as proven by the comparable flow estimates obtained with the two tracers in normal human subjects [22,34]. However, if the tissue composition is highly heterogeneous, as in jeopardized regions, the differences become significant.

![Anesthetized Dog](image1)

Fig. 1. Distribution of regional myocardial blood flow measured with radioactive microspheres in an anesthetized dog at control and during maximal hyperemia induced by intracoronary adenosine. Although mean control flow was 1.58 ml/g/min, the extremes of flow ranged more than threefold (From Austin et al. [26] with permission).

![Normal Human Subjects (n = 160)](image2)

Fig. 2. Distribution of regional myocardial blood flow measured with PET and H$_{15}$O at baseline and during near maximal hyperemia induced by either adenosine or dipyridamole in normal human subjects. It is worth noting the similarities in flow distributions with the example shown in Fig. 1. The heterogeneity in flow distribution across species both at baseline and during hyperemia highlights the difficulty of setting threshold values for normal myocardial blood flow. Adapted from Ref. [29].
myocardium of patients with previous infarction, the flow estimates obtained with these two tracers can show discrepancies. In a highly heterogeneous tissue, the diffusion/extraction and final uptake of $H_{15}O$ and $^{13}NH_3$ are determined by the flow rates in each tissue compartment, i.e. higher in viable tissue and lower in scar tissue. $^{13}NH_3$ uptake in a given region of interest will reflect the average uptake and hence average flow in this mixture of viable and fibrotic tissue. On the other hand, since the uptake of $H_{15}O$ in scar tissue is negligible, washout of $H_{15}O$ will mainly reflect activity in better perfused segments and the resulting flow can therefore be higher than that obtained with $^{13}NH_3$ in the same region [35–37]. Recent refinements of the $H_{15}O$ technique have permitted incorporation of an estimate of the fraction of tissue (perfusable tissue fraction, PTF) within the volume of interest that is exchanging the freely diffusible tracer into the kinetic model [38]. This technique provides values of flow per gram of perfusable tissue and not per gram of region of interest [35,36]. A further accomplishment is the calculation of the perfusible tissue index (PTI), i.e. the ratio of the perfusable tissue fraction to the total tissue mass (anatomic tissue fraction) in the region of interest [35]. Gerber et al. [39] in a parallel assessment of MBF with $H_{15}O$ and $^{13}NH_3$ showed that in normal and reversibly dysfunctional myocardium the two techniques yield similar results whereas discordant findings were observed in persistently dysfunctional segments. These latter are characterized by a significant decrease of PTI and the discrepancies between $H_{15}O$ and $^{13}NH_3$ MBF estimates are smoothed when $H_{15}O$ MBF is corrected for PTI [39].

5.2. The partial volume effect

The loss of systolic wall thickening and presence of scar with wall thinning result in a ‘partial volume effect’ (discussed in more detail previously) that can lead to a 15–25% underestimation of regional radioactivity counts and therefore contribute to the lower MBF computed in these dysfunctional regions. The rectification of the underestimation of myocardial radioactivity due to the partial volume effect and cardiac wall motion is essential for an accurate measure of MBF in cardiac PET studies [40]. However, the correction for ‘partial volume effect’ has not been undertaken in all PET studies in patients with heart failure and hibernating myocardium (see Tables 1–3) [10].

6. PET studies of MBF in patients with hibernating myocardium

The literature can on occasion appear confused, as variable results have been reported in different PET studies [8,41]. There are a number of technical reasons (see above) that affect the various PET studies to different extents and can explain, at least in part, this apparent discrepancy. Moreover, one has to consider the issue of whether flow in hibernating segments should be compared with flow in normally contracting, remote segments in the same patients or with the data obtained in matched normal volunteers.

Therefore, direct comparison of different PET studies must be carefully weighed considering a number of factors: (a) demonstration of functional recovery after revascularization, the latter being the definitive criterion to define a dysfunctional segment subtended by a stenotic artery as ‘hibernating’, (b) the characteristics of the tracer and kinetic model used, and (c) whether appropriate corrections for the calculation of MBF have been applied.

For instance, all the five studies summarized in Table 1 did not include demonstration of functional recovery of dysfunctional myocardium and in most cases correction for partial volume was not applied. The demonstration of

<table>
<thead>
<tr>
<th>Reference</th>
<th>$N$ patients</th>
<th>Previous MI</th>
<th>MBF in remote region (ml/min/g)</th>
<th>MBF in HM region (ml/min/g)</th>
<th>PV correction</th>
<th>Definition of HM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Czernin et al. [68]</td>
<td>22</td>
<td>Y recent 21–170 h before</td>
<td>$0.83 \pm 0.20$</td>
<td>$0.57 \pm 0.20^*$ (range 0.27–0.89)</td>
<td>N</td>
<td>Flow/metabolism mismatch</td>
</tr>
<tr>
<td>Sambuceti et al. [69]</td>
<td>33</td>
<td>N One vessel stenosis</td>
<td>$0.77 \pm 0.26$</td>
<td>$0.66 \pm 0.19^*$ (range 0.43–1.21)</td>
<td>N</td>
<td>Echocardiography</td>
</tr>
<tr>
<td>Sun et al. [70]</td>
<td>19</td>
<td>Y</td>
<td>$0.73 \pm 0.23$ (range 0.45–1.10)</td>
<td>$0.53 \pm 0.33$ (range 0.33–0.87)</td>
<td>Y</td>
<td>Flow/metabolism mismatch Echocardiography—low dose dobutamine</td>
</tr>
<tr>
<td>Brunelli et al. [71]</td>
<td>15</td>
<td>Y 30 days before PET</td>
<td>$0.83 \pm 0.26$</td>
<td>$0.65 \pm 0.27^*$</td>
<td>N</td>
<td>Echocardiography dobutamine Flow/metabolism mismatch</td>
</tr>
<tr>
<td>Marzullo et al. [72]</td>
<td>14</td>
<td>Y 1 vessel</td>
<td>$1.00 \pm 0.24$</td>
<td>$0.69 \pm 14^<em>$ (45% of dyssynergic segments) $0.42 \pm 0.12^</em>$ (19% of dyssynergic segments)</td>
<td>N</td>
<td>Flow/metabolism mismatch</td>
</tr>
</tbody>
</table>

* $P<0.05$ versus remote region.
viability, i.e. flow/metabolism mismatch assessed with $^{13}$NH$_3$ and $^{18}$F-fluorodeoxyglucose (FDG) and PET was taken as *indirect* evidence of hibernation. It must be pointed out that the presence of flow/metabolism mismatch is not necessarily associated with functional recovery after revascularization, the latter being mainly dictated by the amount of fibrotic tissue within the region of interest [42,43]. On the other hand, when demonstration of functional recovery after revascularization is used for the definition of hibernation, both H$_2^{15}$O and $^{13}$NH$_3$ give comparable results. In nine of 15 studies reported in Tables 2 and 3, MBF in hibernating segments was not significantly different from MBF in remote, normally contracting myocardium whereas in six studies a ~20% lower MBF was found in hibernating segments compared to remote myocardium. Although the paired comparison of flow in dysfunctional and remote areas is statistically more powerful than comparing patients with a normal matched population, the data need to be carefully weighed and regional differences in cardiac workload considered.

Table 2
PET studies of MBF using H$_2^{15}$O in patients with hibernating myocardium

<table>
<thead>
<tr>
<th>Reference</th>
<th>N patients</th>
<th>Previous MI</th>
<th>MBF in remote region (ml/min/g)</th>
<th>MBF in HM region (ml/min/g)</th>
<th>PV correction</th>
<th>Functional recovery assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Silva et al. [35]</td>
<td>7</td>
<td>Y acute</td>
<td>0.97±0.28</td>
<td>0.68±0.32* (range 0.46–1.37)</td>
<td>Y</td>
<td>Echocardiography (4 months)</td>
</tr>
<tr>
<td>Conversano et al. [73]</td>
<td>17</td>
<td>Y (11/17)</td>
<td>0.85±0.36</td>
<td>0.65±0.28* (range 0.32–0.25)</td>
<td>N</td>
<td>Echocardiography (2.9±1.1 months)</td>
</tr>
<tr>
<td>Marinho et al. [37]</td>
<td>30</td>
<td>Y (30/30)</td>
<td>0.92±0.25</td>
<td>0.87±0.31</td>
<td>Y</td>
<td>Radionuclide ventriculography (4–6 months)</td>
</tr>
<tr>
<td>Maki et al. [74]</td>
<td>6</td>
<td>N</td>
<td>1.02±0.23</td>
<td>0.81±0.27*</td>
<td>Y</td>
<td>Echocardiography (8±3 months)</td>
</tr>
<tr>
<td>Maki et al. [75]</td>
<td>5</td>
<td>N</td>
<td>0.81±0.15</td>
<td>0.77±0.18 (range 0.64–1.14)</td>
<td>Y</td>
<td>Echocardiography (8–11 months)</td>
</tr>
<tr>
<td>Gerber et al. [39]</td>
<td>16</td>
<td>Y</td>
<td>0.83±0.06</td>
<td>0.74±0.06</td>
<td>Y</td>
<td>Echocardiography (7.5±2.1 months)</td>
</tr>
<tr>
<td>Fath-Ordoubadi et al. [76]</td>
<td>18</td>
<td>N</td>
<td>0.89±0.24</td>
<td>0.82±0.26</td>
<td>Y</td>
<td>Echocardiography (4.2±0.5 months)</td>
</tr>
<tr>
<td>Pagano et al. [61]</td>
<td>22</td>
<td>Y</td>
<td>1.02±0.23</td>
<td>1.02±0.24</td>
<td>Y</td>
<td>Echocardiography (6 months)</td>
</tr>
</tbody>
</table>

* P<0.05 versus remote region.

viability, i.e. flow/metabolism mismatch assessed with $^{13}$NH$_3$ and $^{18}$F-fluorodeoxyglucose (FDG) and PET was taken as *indirect* evidence of hibernation. It must be pointed out that the presence of flow/metabolism mismatch is not necessarily associated with functional recovery after revascularization, the latter being mainly dictated by the amount of fibrotic tissue within the region of interest [42,43]. On the other hand, when demonstration of functional recovery after revascularization is used for the definition of hibernation, both H$_2^{15}$O and $^{13}$NH$_3$ give comparable results. In nine of 15 studies reported in Tables 2 and 3, MBF in hibernating segments was not significantly different from MBF in remote, normally contracting myocardium whereas in six studies a ~20% lower MBF was found in hibernating segments compared to remote myocardium. Although the paired comparison of flow in dysfunctional and remote areas is statistically more powerful than comparing patients with a normal matched population, the data need to be carefully weighed and regional differences in cardiac workload considered.

Table 3
PET studies of MBF using $^{13}$NH$_3$ in patients with hibernating myocardium

<table>
<thead>
<tr>
<th>Reference</th>
<th>N patients</th>
<th>Previous MI</th>
<th>MBF in remote region (ml/min/g)</th>
<th>MBF in HM region (ml/min/g)</th>
<th>PV correction</th>
<th>Functional recovery assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanoverschelde et al. [44]</td>
<td>26</td>
<td>N</td>
<td>0.95±0.27</td>
<td>0.77±0.25*</td>
<td>Y</td>
<td>Contrast ventriculography 12/26 (5–8 months)</td>
</tr>
<tr>
<td>Vanoverschelde et al. [43]</td>
<td>19</td>
<td>Y</td>
<td>0.77±0.18</td>
<td>0.82±0.29</td>
<td>Y</td>
<td>Echocardiography (10 days to 2–6 months)</td>
</tr>
<tr>
<td>Gerber et al. [77]</td>
<td>24</td>
<td>Y</td>
<td>0.82±0.22</td>
<td>0.84±0.27</td>
<td>Y</td>
<td>Echocardiography (5±1.9 months)</td>
</tr>
<tr>
<td>Gerber et al. [39]</td>
<td>16</td>
<td>Y</td>
<td>0.77±0.04</td>
<td>0.84±0.08</td>
<td>Y</td>
<td>Echocardiography (7.5±2.1 months)</td>
</tr>
<tr>
<td>Grandin et al. [78]</td>
<td>19</td>
<td>Y (6/17)</td>
<td>0.98±0.18</td>
<td>0.75±0.20* (range 0.45–1.10)</td>
<td>Y</td>
<td>Contrast ventriculography (6 to 9 months)</td>
</tr>
<tr>
<td>Kitsiou et al. [79]</td>
<td>26</td>
<td>Not reported</td>
<td>0.64±0.24</td>
<td>0.63±0.27</td>
<td>N</td>
<td>Radionuclide angiography (10/26) MRI (16/26), (2.5±0.8 months PTCA) (5.8±8.8 months CABG)</td>
</tr>
<tr>
<td>Maes et al. [63]</td>
<td>14</td>
<td>Y</td>
<td>0.94±0.11*</td>
<td>0.64±0.12</td>
<td>Y</td>
<td>Radionuclide angiography (3 months)</td>
</tr>
</tbody>
</table>

* P<0.05 versus remote region.
difference observed might be explained, at least in part, by a higher MBF in the remote normally contracting regions rather than by an absolute reduction in hibernating segments. The latter would be consistent with the higher oxygen consumption reported in regions remote from segments with severe wall motion abnormalities [44].

7. Transmural distribution of myocardial blood flow

In the presence of marked spatial tissue heterogeneity, such as occurs in patients with coronary artery disease and chronic left ventricular dysfunction, the measured flow value may represent a transmural average between several values ranging from very low in necrotic subendocardial areas to normal in well perfused subepicardial regions. In fact, it must be recognized that MBF rates <0.60 ml/min/g, compatible with a reduced resting perfusion, have been found in a small fraction (about 10%) of hibernating segments [9,37]. Admittedly, the limited spatial resolution of the PET scanners used in most studies allows only measurement of average transmural (i.e. full thickness) MBF. In the absence of flow restriction, subendocardial layers tend to have less flow than subepicardial layers. Therefore, a small reduction in average flow across the wall may still correspond to a more severe reduction in subendocardial blood flow. Whether or not subendocardial blood flow is reduced in patients with hibernating myocardium awaits verification by direct measurement [45]. However, using the worst case scenario (zero reduction in subepicardial blood flow with ischemia), a 20% reduction in transmural flow results in a 40% reduction in subendocardial blood flow and accounts for less functional impairment then seen in most patients with hibernating myocardium [46–48].

8. Coronary flow reserve and hibernation

The coronary flow reserve is the ratio of MBF during near maximal vasodilatation (pharmacologically-induced) to resting MBF and is an index of the functional significance of coronary stenoses. In patients with coronary artery disease, flow reserve decreases in proportion to the degree of stenosis severity and is abolished (i.e. hyperemic MBF/resting MBF) for stenoses >80% of the luminal diameter [49,50]. Under these circumstances, any increase in cardiac workload above baseline conditions cannot be met by an adequate increase in MBF, leading to ischemia. Therefore, in patients with severe coronary artery disease the limited flow reserve leads to the development of myocardial ischemia, which is often asymptomatic [51] even for small increases of oxygen demand such as those associated with ordinary daily activities [52]. Regardless of the blood flow level under baseline conditions, these patients will develop ischemia when oxygen demand is increased (demand ischemia).

Myocardial ischemia is invariably associated with the development of post-ischemic contractile dysfunction that persists following reperfusion despite the restoration of normal or near-normal coronary blood flow. In the mid-1970s, this phenomenon, later on known as myocardial stunning [53], was initially described by Heyndrickx et al. [54] as a sustained, but eventually completely reversible post-ischemic contractile dysfunction in a conscious healthy dog model subjected to a 15-min coronary occlusion. Two decades later it has been shown that patients with chronic coronary artery disease and absence of contractile dysfunction at rest may also develop myocardial stunning after induction of ischemia with exercise or dobutamine [55–57]. MBF was measured using PET and H15O in patients with CAD and normal LV function. Global (EF) and regional LV systolic function (SF) were measured using quantitative echocardiography during and after dobutamine-induced ischaemia [57]. The results of this study show that EF and SF were reduced 30 min after dobutamine, but recovered by 120 min. MBF (ml/min/g) to regions with reversible LV dysfunction was normal at baseline and during dysfunction (0.88 and 1.09 ml/min/g, respectively, P=NS). In conclusions, in patients with CAD, dobutamine produces prolonged, but reversible LV dysfunction when MBF is normal, thus confirming the occurrence of stunning.

In addition, we have recently demonstrated that in patients with stable exercise-inducible ischemia and normal ventricular function, repeated episodes of ischemia may be cumulative and culminate in more prolonged and severe post ischemic stunning [58] (Fig. 3).

Thus, in the long term, intermittent episodes of ischemia followed by stunning might induce regional alterations in the myocytes thus contributing to the development of persistent, but still reversible left ventricular dysfunction [44,59]. Clearly, under these conditions, coronary revascularization by restoring flow reserve could interrupt the vicious circle that has led to chronic ischemic dysfunction [60,61] (Fig. 4).

Preoperative resting flow values are not the best predictors of functional improvement after revascularization [62,63]. The prognosis depends more on ultrastructural [63,64] and metabolic [62] integrity of the myocytes. The presence and extent of functional recovery is inversely related to the amount of fibrosis [42,63]. Concurrently, the processes of transcription and translation aimed at repairing nuclear and mitochondrial abnormalities, loss of contractile material and disorganization of cytoskeleton all affect the time course of functional recovery [43,64].

In a recent study, Vanoverschelde et al. [43] showed that adequate revascularization is not always sufficient for subsequent complete recovery; successful revascularization was achieved in all patients, but only 19/32 had an improved function at 6 months. In those patients the extent
of recovery was determined by a combination of several independent factors such as: MBF (¹³NH₃), end-diastolic volume, glucose uptake and the proportion of extracellular matrix.

9. Concluding remarks

If one considers the PET MBF studies in patients with hibernating myocardium based on the criteria discussed in the present review article, the following conclusions can be reached: (a) in the majority of these studies resting MBF in hibernating myocardium is not different from either flow in remote tissue in the same patient or MBF in normal healthy volunteers; (b) a reduction in MBF of ~20% compared to MBF in remote myocardium or age matched normal subjects has been demonstrated in a minority of truly hibernating segments; (c) hibernating myocardium is characterized by a severely impaired coronary flow reserve which improves after revascularization in parallel with contractile function.

Altogether, the available studies indicate that the pathophysiology of hibernation is more complex than initially postulated [7]. The recent evidence that repetitive ischemia in patients with coronary artery disease can be cumulative and lead to more severe and prolonged stunning, lends further support to the hypothesis that, at least initially, stunning and hibernation are two facets of the same coin (functional hibernation) while later on the condition becomes associated with a different phenotype (structural hibernation) [65]. This would explain the speed with which functional improvement takes place in different patients that correlates with the degree of tissue degeneration [43].

In addition, a similar pattern of ventricular dysfunction and tissue alteration have been recently reported in a porcine model with a chronic fixed coronary stenosis which is characterized by an initial impairment of flow reserve followed by a slightly reduced (~20%) resting flow [66].

Finally, because of the tight link between myocardial function and MBF, simultaneous accurate determination of regional myocardial function would be important to gain further insight into the heterogeneity of regional MBF. In
addition, further studies with higher sensitivity/resolution PET scanners [67] are needed to ascertain whether hibernating myocardium is characterized by a selective reduction of MBF in the subendocardial layers of the left ventricle.

References


