

## H

4 270M Hb 78 ↑ SV  
HAEM IRONS PER HB MOLECULE HB MOLECULES PER RED CELL/G/L — OUR PATIENT'S LEVEL COMPENSATORY STROKE VOLUME RISE

## The quiet thief

Breathlessness frightens people. When a patient arrives worried they cannot climb a hill without stopping, the first thought — for them and their doctor — often turns to the heart. Could it be a blocked artery? A failing valve? A clot on the lung? These are the dramatic diagnoses, and they deserve to be ruled out promptly. But sometimes the answer is quieter, older, and entirely treatable: the blood simply cannot carry enough oxygen.

Iron deficiency anaemia is one of the most common conditions on the planet, and one of the most underestimated. It does not announce itself with chest pain or a collapsing blood pressure. It creeps. Fatigue first, then breathlessness on exertion, then a heart that must work harder and faster just to keep the tissues alive. Left long enough, it can generate a heart murmur in a patient who never had one before.

This is the story of how that happens — told through physiology, through the cellular life of iron, and through the case of a patient I saw recently who arrived breathless, anxious, and carrying a murmur nobody had expected.

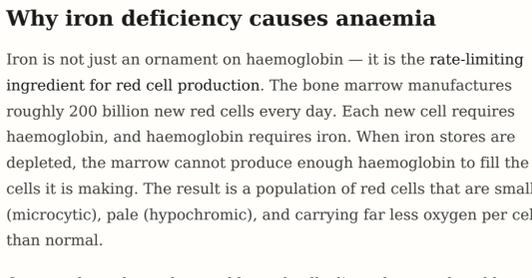
*"The red cell is, at its core, a bag of haemoglobin. And haemoglobin is, at its core, a scaffold built around iron."*

## The red cell's only job

The red blood cell is the most specialised cell in the human body. It has no nucleus, no mitochondria, no capacity for its own energy production. It has sacrificed everything to do one thing with extraordinary efficiency: carry oxygen from the lungs to the tissues and return carbon dioxide in the opposite direction.

At the heart of this function is haemoglobin — the iron-containing protein that occupies 97% of a red cell's dry weight. Each haemoglobin molecule is made of four protein chains (the globins), each carrying a haem group. And at the centre of each haem group sits a single atom of iron in the ferrous ( $\text{Fe}^{2+}$ ) state. It is this iron atom that forms a reversible bond with oxygen in the lungs, and releases it to hungry tissues where oxygen tension is low.

One red blood cell carries approximately 270 million haemoglobin molecules. Each haemoglobin molecule can carry four oxygen molecules — one per iron atom. The arithmetic of oxygen delivery in a healthy person is staggering. When iron is depleted, that arithmetic fails.



## Why iron deficiency causes anaemia

Iron is not just an ornament on haemoglobin — it is the rate-limiting ingredient for red cell production. The bone marrow manufactures roughly 200 billion new red cells every day. Each new cell requires haemoglobin, and haemoglobin requires iron. When iron stores are depleted, the marrow cannot produce enough haemoglobin to fill the cells it is making. The result is a population of red cells that are small (microcytic), pale (hypochromic), and carrying far less oxygen per cell than normal.

Over weeks and months, as older red cells die and are replaced by these iron-poor newcomers, the total oxygen-carrying capacity of the blood falls. The haemoglobin concentration — the standard clinical measure — drops below normal. Once it falls below about 100 g/L, most people begin to notice something is wrong. Below 80 g/L, the body is in genuine physiological stress.

But iron does more than build haemoglobin. It is a co-factor for cytochrome enzymes in the mitochondrial electron transport chain — the machinery that generates ATP, the energy currency of every cell. The heart muscle cells (cardiomyocytes) are among the most mitochondria-rich cells in the body, running almost entirely on oxidative phosphorylation. In severe iron deficiency, even if you corrected the anaemia with a blood transfusion, cardiac muscle cells would still be functionally impaired — starved of the iron they need to generate energy at a cellular level. This is why intravenous iron has been shown to improve exercise capacity and symptoms in heart failure patients even when their haemoglobin is only mildly reduced.

### OXYGEN DELIVERY FAILURE

Fewer iron-loaded haem sites mean less  $\text{O}_2$  transported per unit of blood. Tissues signal hypoxia; the cardiovascular system compensates by increasing output.

### CELLULAR ENERGY FAILURE

Iron-dependent cytochrome enzymes in cardiac mitochondria falter. The heart pumps harder — but with less biochemical efficiency per beat.

## How the heart compensates — and why that matters

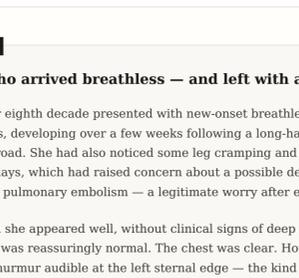
The body's response to anaemia is elegant, rapid, and ultimately self-defeating if the cause is not treated. When oxygen delivery falls, tissue chemoreceptors signal distress. The autonomic nervous system responds by increasing heart rate and — crucially — increasing stroke volume: the amount of blood ejected with each heartbeat.

This compensatory increase in stroke volume is achieved through the Frank-Starling mechanism: the heart fills more completely with each diastole, stretching the ventricular walls, and this stretch translates into a more powerful systolic contraction. The cardiac output — the product of heart rate and stroke volume — rises to try to compensate for the reduced oxygen content of each millilitre of blood.

For a time, this works. The patient feels breathless only on significant exertion. As the anaemia worsens, the compensation fails to keep pace, and breathlessness appears at lower and lower levels of activity. The heart is now under sustained haemodynamic stress: an enlarged, overworked chamber, hyperdynamic, inefficient, and — here is where it gets interesting from a cardiologist perspective — producing dramatically increased blood flow velocity across the cardiac valves.

### Why severe anaemia produces a heart murmur

Heart murmurs arise when blood flow becomes turbulent rather than laminar. Turbulence is governed by the Reynolds number — a function of flow velocity, vessel diameter, and blood viscosity. In significant anaemia, two of these three factors shift simultaneously in the direction of turbulence: flow velocity rises (because stroke volume increases) and blood viscosity falls (because the red cell count is low — the blood is literally more watery).



The result is a soft, blowing, systolic murmur — typically loudest at the left sternal edge or pulmonary area — in a patient who may have had a silent, competent aortic or pulmonary valve before the anaemia developed. This is called a flow murmur or haemic murmur. It is not a sign of structural valve disease; it is a sign of the haemodynamic stress the heart is under.

The same mechanism can mislead in a patient with known mild aortic stenosis. A mildly narrowed valve may be clinically insignificant at normal cardiac output. Add significant anaemia, drive up stroke volume, and the velocity across that already-narrowed orifice rises further. The pressure gradient across the valve increases, the murmur becomes louder and harsher, and an echocardiogram may suddenly grade the stenosis as more severe than it truly is when the anaemia is corrected. This is an important diagnostic trap: always correct haemoglobin before grading the severity of aortic stenosis.

### CLINICAL CASE

#### A patient who arrived breathless — and left with answers

A woman in her eighth decade presented with new-onset breathlessness on hills and palpitations, developing over a few weeks following a long-haul flight and a brief illness abroad. She had also noticed some leg cramping and mild swelling in the preceding days, which had raised concern about a possible deep vein thrombosis and pulmonary embolism — a legitimate worry after extended travel.

On examination she appeared well, without clinical signs of deep vein thrombosis. Blood pressure was reassuringly normal. The chest was clear. However, there was a soft systolic murmur audible at the left sternal edge — the kind of quiet, blowing sound that could easily be dismissed but deserved explanation.

A D-dimer was low, effectively excluding clinically significant active thrombosis. BNP was normal for her age, making cardiac failure very unlikely. A pulmonary embolism or a new coronary event were both considered and set aside with confidence. The ECG was entirely normal.

Blood tests told a different story. The preliminary full blood count returned:

HAEMOGLOBIN <b>78 g/L</b> Normal: 115–165
HAEMATOCRIT <b>26.5%</b> Normal: 37–47%
RED CELL COUNT <b>2.78</b> Normal: $3.80\text{--}5.80 \times 10^9/\text{L}$
SERUM IRON <b>3.7 <math>\mu\text{mol/L}</math></b> Normal: 5.8–34.5
TRANSFERRIN SAT. <b>6.6%</b> Normal: 15–50%
ALBUMIN <b>32 g/L</b> Normal: 35–50

This was not mild iron deficiency. A haemoglobin of 78 g/L with a transferrin saturation of 6.6% represents severe, established iron depletion. The murmur was immediately explained: her heart had compensated for months of falling oxygen delivery by driving up stroke volume, and the resulting turbulent flow across an otherwise normal aortic valve was producing exactly the soft systolic murmur we heard.

The cause of the iron deficiency — whether through blood loss, malabsorption, or both — required investigation in its own right. Given a family history of colorectal cancer and recently worsening dyspepsia, she was referred urgently for upper and lower GI endoscopy alongside intravenous iron therapy to correct the deficiency rapidly. The breathlessness, the palpitations, and almost certainly the murmur will resolve as her haemoglobin recovers.

### The cellular logic: why iron matters beyond blood

- Mitochondrial electron transport. Cytochrome c, cytochrome oxidase (Complex IV), and the Rieske iron-sulphur protein in Complex III all require iron as a structural and redox co-factor. Without iron, ATP synthesis stalls.

- Myoglobin. Cardiac and skeletal muscle contain myoglobin — a single-chain haem protein that stores and rapidly releases oxygen within the cell. It is the intracellular oxygen buffer. Iron depletion reduces myoglobin, removing this reserve.

- Ribonucleotide reductase. This iron-dependent enzyme is essential for DNA synthesis and therefore red cell production itself. Deficiency feeds back to impair the marrow's ability to mount a corrective response.

- Nitric oxide signalling. Iron participates in NO synthesis and sensing. In iron deficiency, vascular tone regulation is subtly impaired — contributing to the hyperdynamic circulation that underpins the flow murmur.

## The diagnostic lesson

New breathlessness in an older patient demands a systematic approach. The cardiovascular causes — coronary artery disease, heart failure, aortic stenosis, pulmonary embolism — must be excluded efficiently and without undue delay. But anaemia belongs on that differential from the first moment, not as an afterthought once the echocardiogram has been reported normal.

The presence of a murmur in a breathless, anaemic patient is not a contradiction to be explained away. It is the physiology speaking clearly: this heart is working too hard, and it is telling you so with every turbulent systole. The murmur is not the problem. The iron deficiency is.

And iron deficiency always has a cause. Detecting it is the beginning of the investigation, not the end. Dietary insufficiency, occult gastrointestinal bleeding, coeliac disease, menstrual loss in younger women — each requires its own approach. In an older patient with worsening dyspepsia and a family history of bowel cancer, the urgency of upper and lower endoscopy needs no justification. The blood count has just handed us a diagnostic opportunity we must not waste.

## Key take-home points

- Iron is the backbone of oxygen transport. Without it, haemoglobin cannot be loaded with  $\text{O}_2$ , and oxygen delivery to tissues — including the heart itself — falls.
- The heart compensates by increasing stroke volume. This hyperdynamic state is a direct physiological response to reduced oxygen content per unit of blood.
- Severe anaemia produces a systolic flow murmur through increased blood velocity and reduced viscosity, even across a structurally normal valve. The murmur resolves when the anaemia is corrected.
- Do not grade aortic stenosis in the presence of significant anaemia. The pressure gradient will be inflated by the raised cardiac output and will overestimate true structural severity.
- Iron deficiency is never a diagnosis in itself. Its cause must always be sought — and in older patients with GI symptoms or family history, the threshold for endoscopy should be low.
- Intravenous iron corrects the deficiency rapidly and is the treatment of choice when oral iron is poorly tolerated or urgency demands faster repletion.

Published by Edward Leatham, Consultant Cardiologist, Surrey Cardiovascular Clinic. This article is written for educational purposes and does not constitute individual medical advice. Patients with new breathlessness or palpitation should seek clinical assessment. The clinical case described has been anonymised with identifying details removed.